AN ABSTRACT OF THE THESIS OF

Hyunik Shin for the degree of Doctor of Philosophy in Chemistry presented on January 11, 1994.

Title: An Approach Toward the Synthesis of Euonyminol and Cathedulin K-19.

Abstract approved by: Redacted for Privacy

A synthetic approach toward the two major fragments of cathedulin K-19, euonyminol (**4**) and dimethyl cathate (**69**), was investigated. Synthesis of dimethyl cathate was accomplished in 3 steps starting from **73**. Efforts directed towards the synthesis of euonyminol, a highly oxygenated dihydroagarofuran sesquiterpene, was advanced to a stage in which most of the A ring of **4** was completed. Compound **79** was used as a starting material which was obtained from a Diels-Alder reaction of **80** and **81**. Subsequent bromination of **79** and elimination of hydrogen bromide afforded **93** in a one-pot operation. A remarkable chemo- and stereoselective reduction of **93** under Luche conditions gave **94** and the latter was epoxidized stereoselectively by *m*-chloroperbenzoic acid to yield **91**. Introduction of an isopropenyl moiety to **91** was accomplished following Liotta's protocol to provide **145**. Vanadium catalyzed epoxidation installed the epoxide moiety of **152a** with good stereoselectivity. Two approaches towards **4** from the key intermediate **152a** were pursued. The first approach entailed the epoxide cascade reaction of **152a**. Treatment of **152a** with trifluoro- or trichloroacetic acid afforded **165** and **166**, respectively, which possessed most of the functionality required for **4**. The second route to **178**

proceeded in 5 steps from **152a**. Treatment of **152a** with titanium tetraisopropoxide afforded **168**, which was cyclized to **169** under acid catalysis. The diol moiety of **169** was protected as a benzylidene acetal and subsequent hydroxylation following Davis' procedure afforded **171**. Stereoselective reduction of **171** using lithium aluminum hydride in the presence of titanium tetraisopropoxide provided **178**.

An Approach Toward the Synthesis of Euonyminol and Cathedulin K-19

By

Hyunik Shin

A THESIS

submitted to

Oregon State University

in partial fulfillment of
the requirements for the
degree of

Doctor of Philosophy

Completed January 11, 1994

Commencement June 1994

APPROVED:

Redacted for Privacy

Professor of Chemistry in charge of major

Redacted for Privacy

Chair of Department of Chemistry

Redacted for Privacy

Dean of Graduate School

Date thesis is presented January 11, 1994

Thesis prepared by Hyunik Shin

To Haegyung, Chaehee, and Jaesoon

Acknowledgements

I would like to sincerely thank professor James D. White for the support and guidance that made this thesis possible. I would also like to thank the present and past members of the White group, particularly Frank Stappenbeck, No-soo Kim, Tae-seong Kim, Scott Jeffery, Mark Jensen, Neal Green, Steve Perri, Steve Toske for their friendship and helpful discussions.

I thank Frank Stappenbeck for X-ray crystallographic analyses and Rodger Kohnert for his advice and assistance on the NMR analyses.

The National Institutes of Health and Benedict fund are acknowledged for financial support.

Finally, I thank my wife for her love and patience and Sung-bum for unconditional support all through my stay in the United States.

TABLE OF CONTENTS

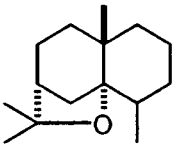
LIST OF FIGURES

LIST OF TABLES

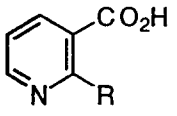
An Approach Toward the Synthesis of Euonyminol and Cathedulin K-19

Introduction

Plants of the family Celastraceae produce a variety of chemically and biologically interesting secondary metabolites. In particular, maytansine[1] isolated from *Matenus ovatus* and triptolide[2] from *Tripterygium wilfordii* have attracted a great deal of attention due to their antitumor activity. However, the most frequently encountered class of natural products produced by plants of this family is based on the dihydroagarofuran framework. The dihydroagarofuran nucleus **1** exists at various oxidation levels and its hydroxylated derivatives are often found in nature esterified with certain alkaloids.[3] These structures all contain either a nicotinate or substituted nicotinate **2**, along with ester groups which include benzoate, acetate, and 3-furoate.



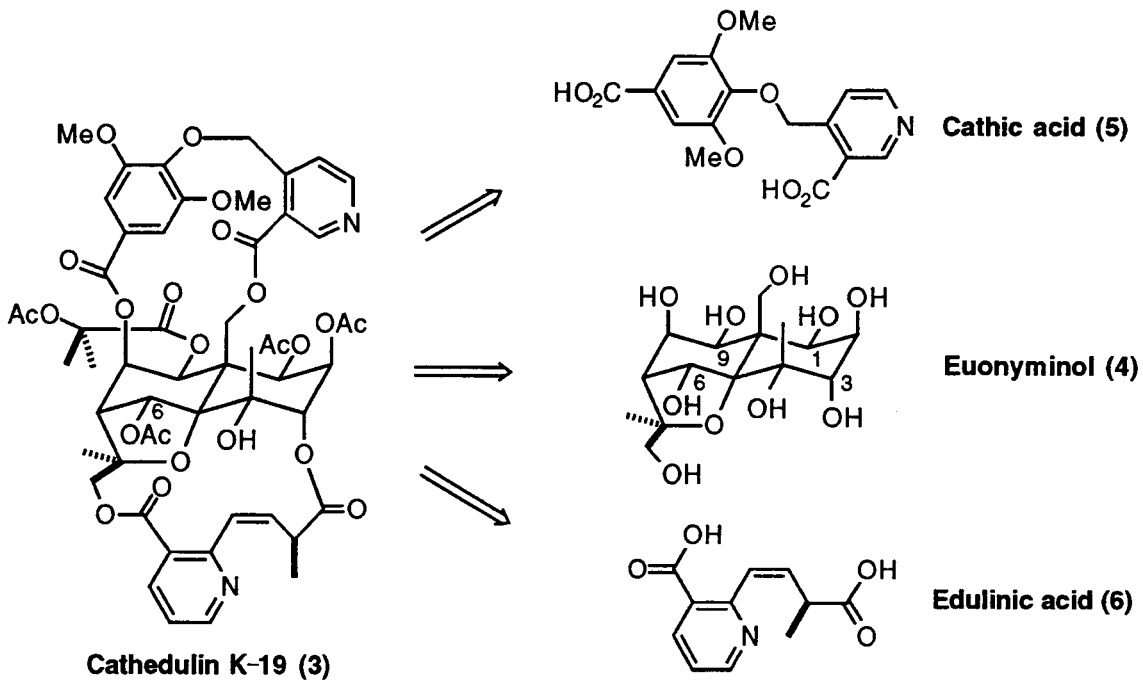
1



2

Several weakly basic alkaloids named cathedulins[4] have been isolated from *Catha edulis*, a member of the Celastraceae. The cathedulins comprise a family of over fourteen macrolide - alkaloids of which K-19 (**3**)[5] is the most highly articulated member. Although the biological activity of K-19 is not known, its structure presents a challenging target in terms of organic synthesis. This thesis

describes efforts toward the synthesis of cathedulin K-19, and more specifically toward the two major fragments, euonyminol (**4**) and cathic acid (**5**).

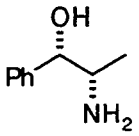


Scheme 1

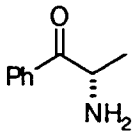
The tree *Catha Edulis* (Forsk) (Celastraceae) is approximately 3 m high and is widely cultivated in parts of East Africa and the southern part of Arabia. It is the source of a drug known as khat.[6] The first account of the effects of khat appeared more than seven centuries ago in an Arabic medical treatise, in which the leaves were recommended to soldiers and messengers for suppressing the feeling of fatigue and hunger.[7] Today, several million people use khat daily because of its stimulating effects, which usually results in moderate euphoria, mild excitement, and an increased alertness and energy, and because of its appetite suppressing properties. Habitual use of khat over many years causes psychic dependence and can lead to personality disorder and to an impairment of overall mental health. It also causes malnutrition due to its appetite

suppressing effect. The drug is generally administrated by chewing young fresh leaves or tender twigs, although infusion or smoked material has been employed occasionally. Being a more profitable crop than coffee, khat has displaced this traditional agricultural product in some parts and its trafficking is continuing to expand as an article of commerce. Despite its stimulant properties, its use is acceptable to Islam.

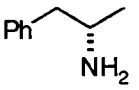
The chemistry of the khat alkaloids mainly involves two groups, the phenylalkylamines and the complex polyesters of polyhydroxylated agarofurans (the cathedulins). Triterpenoids have also been isolated from the neutral component of khat.[8] Although the first attempt to isolate the active principle of the leaves of *Catha edulis* was made a century ago,[9] it was not until 1930 that Wolfes identified cathine (**7**) ((+)-norpseudoephedrine), i.e., (*S,S*)-(+)-phenylpropanolamine among the metabolites of the plant.[10] Soon afterwards, it was found that cathine is a stimulant of rather low potency and that the amount of cathine present in khat is insufficient to account for the symptoms observed after its consumption.[11] In 1980 a more potent stimulating principle was isolated from fresh material by Szendrei and shown to be cathinone (**8**), i.e., (*S*)-(-)-aminopropiophenone.[12] Later it was found that cathinone is a biosynthetic precursor of cathine (**7**) and that this intermediate accumulates in young, but not in adult leaves.[13] After its identification, intensive studies[14] of the pharmacological effects of cathinone (**8**) were carried out which showed that this substance is the major active component of khat. It was shown that cathinone stimulates the central nervous system (CNS) via a mechanism of action similar to that of amphetamine (**9**).



cathine (**7**)



cathinone (**8**)



amphetamine (**9**)

In addition to the phenylalkylamine alkaloids, khat contains the less basic cathedulin alkaloids. The major contribution to the structure elucidation of the latter group was made by Crombie and coworkers, who isolated and formulated the structures of at least 14 cathedulin alkaloids. All of the cathedulins isolated up to the present are polyesters of one of two polyol sesquiterpene frameworks, the pentahydroxyagarofuran **10** and euonyminol (**4**) (**Figure 1**). The latter is more common. Many of the cathedulin alkaloids exist as macrocyclic dilactones in which evoninic (**14**) or edulinic acid (**6**) are coupled to the C-3 and C-12 hydroxyl groups of euonyminol. The remaining hydroxyl groups are esterified with acetic, benzoic, 2-hydroxyisobutyric, 2-acetoxyisobutiric, nicotinic (**11**), or tri-O-methylgallic acid (**13**). In a few of the cathedulin structures cathic acid (**12**) forms a second macrocyclic dilactone with the C-8 and C-15 hydroxyl groups of euonyminol. The structural feature common to the dilactone component of these alkaloids is that the aliphatic terminus of a pyridinedicarboxylic acid is connected by an ester linkage with the C-3 hydroxyl group, and the aromatic acid esterifies the C-12 hydroxyl group. Since an excellent review[4] on the cathedulins has been published, only a brief discussion of the structural features of these and other Celastraceaeous alkaloids based on euonyminol will be presented in this section.

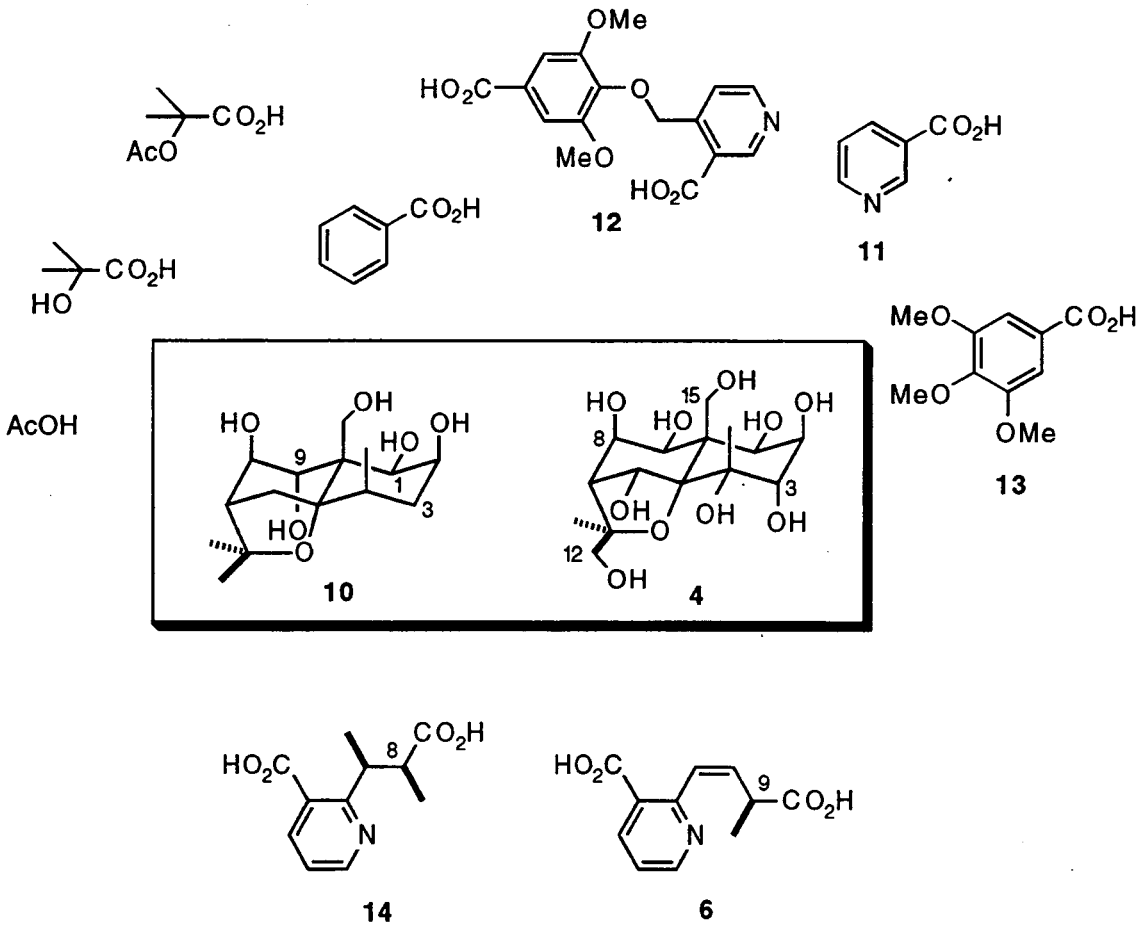
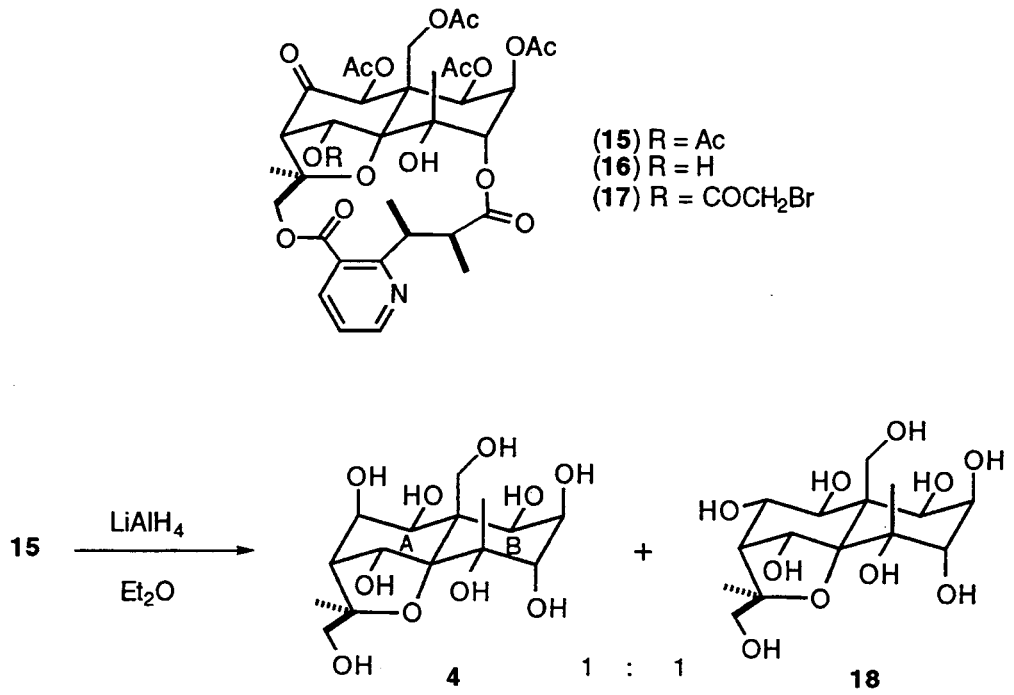


Figure 1: Esterifying Acids of the Sesquiterpene Cores of Cathedulin Alkaloids.

Although Crombie's group deserves most of the credit for unravelling structural details of the cathedulin alkaloids, earlier work on the structural elucidation of alkaloids from other members of the Celastraceae (*euonyminous sieboldianus* and *europaus*) made an important contribution to this field. In particular, Hirata's group, along with the Pailer group successfully elucidated the structure of evonine (**15**) and neoevonine (**16**) (**Scheme 2**).[15] A single crystal X-ray analysis of bromoacetylneoevonine (**17**) as its monohydrate confirmed all stereochemical details including its absolute configuration.[16] The absolute configuration of the sesquiterpene polyol core units of cathedulin and other Celastraceaeous alkaloids is assumed to be the same as for **17**.

Subsequently, Yamada and coworkers identified euonyminol (**4**) from the reduction of evonine (**15**) by lithium aluminum hydride, which afforded both **4** and isoeuonyminol (**18**).[17] In 1977 an unambiguous structure determination of euonyminol was accomplished by X-ray analysis[18] which showed that the B ring of **4** adopts a chair conformation whereas the A ring exists in a distorted chair conformation.

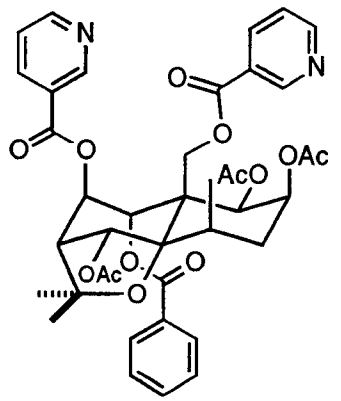


Scheme 2

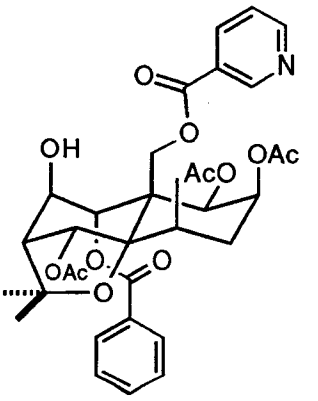
Cathedulins can be conveniently divided into three groups based on their molecular weight. The low molecular weight group includes E-2 (**19**) and E-8 (**20**),[19] both based on the core structure **10** . The medium molecular weight group (750~900) includes K-1 (**21**), K-2 (**22**), K-6 (**23**), K-15 (**24**)[20] and are all based on the euonyminol nucleus in which two of the nine hydroxyl groups are linked to a dicarboxylic acid to form a macrocyclic dilactone. The high molecular weight (1100~1200) group includes E-3 (**27**), E-4 (**28**), E-5 (**29**), E-6

(**30**), K-12 (**32**), K-17 (**33**), K-19 (**3**), and K-20 (**31**).[21,5] They are also based on euonyminol and contain one or two macrocylic dilactone moieties together with other esterifying acids.

As mentioned above, cathedulin E-2 (**19**) and E-8 (**20**) are based on the modified agarofuran core structure **10**. E-8 differs from E-2 only by the absense of nicotinyl substitution at the C-8 hydroxyl group. This has led to the suggestion that E-8 is merely the result of hydrolysis of E-2 during isolation. However, careful hydrolysis of E-2 using triethylamine in methanol afforded 8,15-bisdenicotinylated product and a little E-8 (**20**). Under the conditions using sodium bicarbonate in methanol, all of the ester functions were removed except the benzoate at C-9. Therefore, these experiments provide evidence that E-8 is not an artifact of E-2 during isolation.[18]



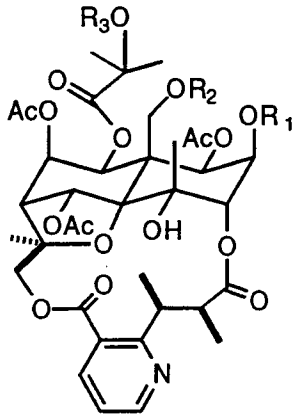
E-2 (19)



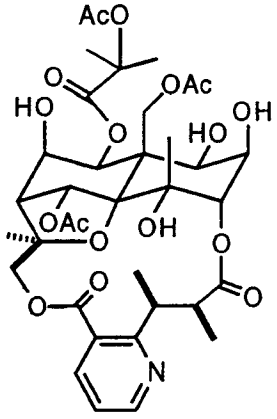
E-8 (20)

The medium molecular weight cathedulins comprising K-1 (**21**), K-2 (**22**), K-6 (**23**), and K-15 (**24**) differ from one another in the degree of esterification at the C-2 and C-15 positions. K-6 lacks acetyl substitution at the C-15 hydroxyl group present in K-2, the latter being related in the same way to K-1 by the absence of acetyl substitution at the C-2 hydroxyl group. K-15 is the only

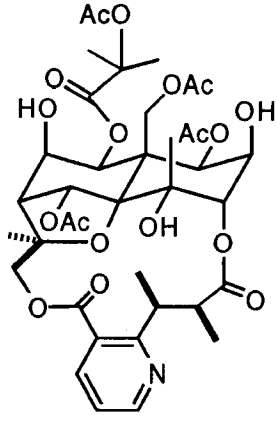
cathedulin alkaloid in this group containing 2-hydroxyisobutyric acid as an esterifying ligand. It is noteworthy that the deacetylation of K-2 did not produce K-6 and K-15 but isomeric structures **25** and **26**, thereby providing evidence that K-6 and K-15 are not artifacts.[19]



	R_1	R_2	R_3
Cathedulin K-1 (**21**)	Ac	Ac	Ac
Cathedulin K-2 (**22**)	H	Ac	Ac
Cathedulin K-6 (**23**)	H	H	Ac
Cathedulin K-15 (**24**)	H	H	H



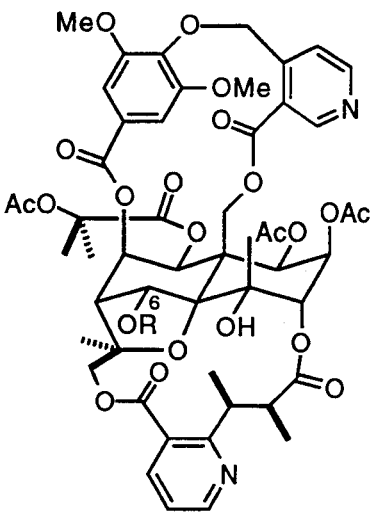
25



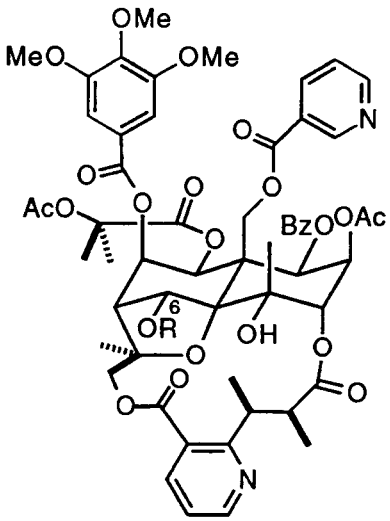
26

The high molecular weight cathedulins E-3 (**27**) and E-4 (**28**) are closely related; acetylation of E-4 gives E-3 and partial hydrolysis of E-3 gives E-4. Both E-3 and E-4 are bismacrocyclic dilactones with cathic and evoninic acids bridging the euonyminol core. Cathedulin E-5 (**29**) and E-6 (**30**) are related to each other in the same way that E-3 and E-4 are related. Indeed, E-5 is produced on acetylation of E-6. A minor cathedulin, K-12 (**32**), was isolated

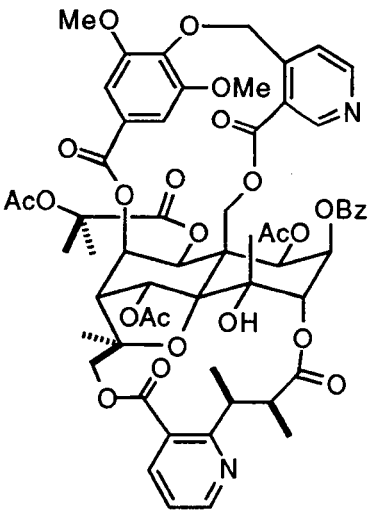
which differs from E-5 only by replacement of the C-1 benzoate group with acetate. K-20 (**31**) is related to E-3 by a different esterifying ligand at C-2, in this case benzoate replacing acetate.



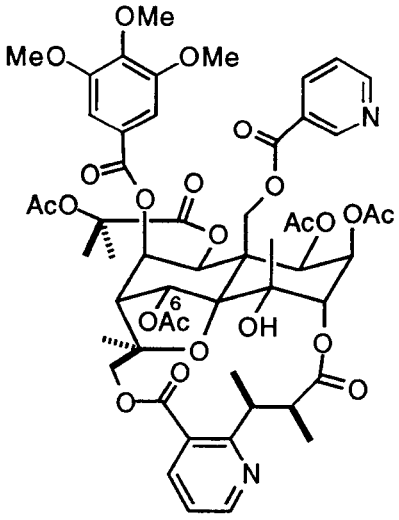
E-3 (27) R = Ac
E-4 (28) R = H



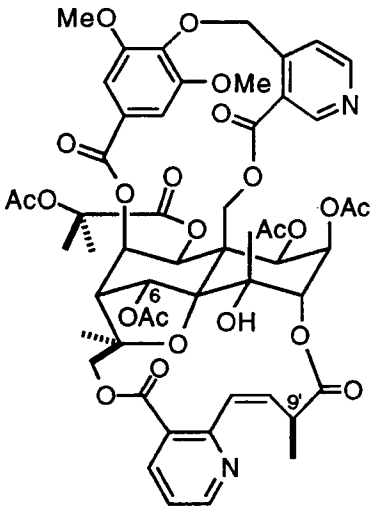
E-5 (29) R = Ac
E-6 (30) R = H



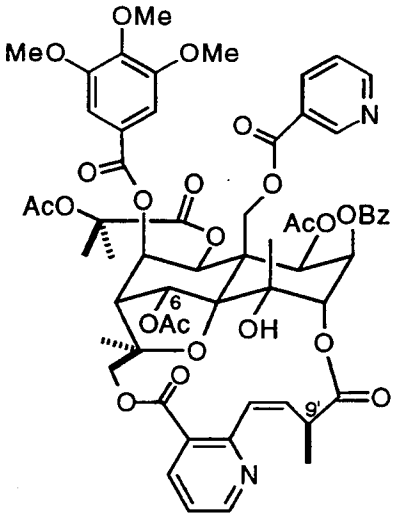
K-20 (31)



K-12 (32)

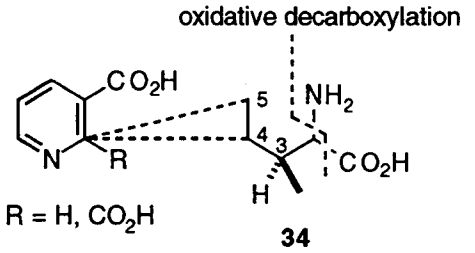


K-19 (3)



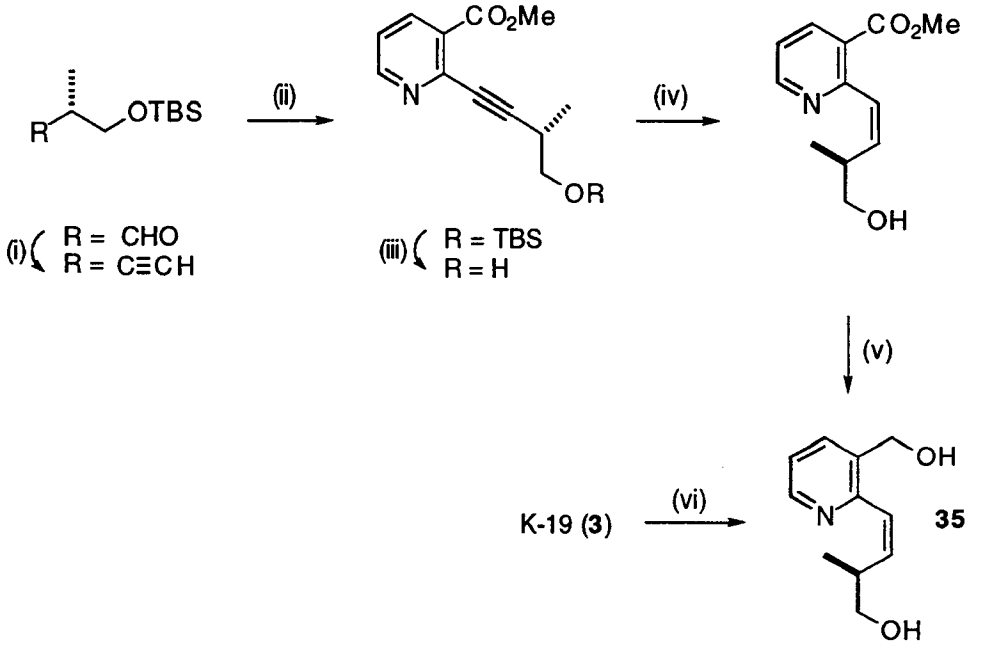
K-17 (33)

Cathedulin K-19 (**3**) and K-17 (**33**) are unique among the cathedulin alkaloids in possessing the edulinic acid (**6**) moiety, a new diacid which forms the lower macrocyclic dilactone ring. Although the stereochemical assignments made for K-17 and K-19 are complete in all other aspects, the stereogenicity at C-9' was left undetermined. The absolute configuration of the C-9 position of edulinic acid was tentatively proposed to be (*S*) based on a hypothetical biosynthetic pathway for its formation.[5] Evoninic and edulinic acid reportedly share the same biogenetic origin from isoleucine (**34**), and both may be viewed as products of coupling at the C-2 position of nicotinic acid with either the C-4 or C-5 position of an intermediate derived from isoleucine. In accord with this hypothesis, the absolute configuration at C-3 of **34** is found to be the same as at C-8 of evoninic acid (**14**) and the same (*S*) configuration is assumed for edulinic acid.



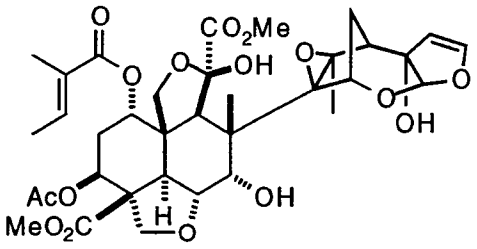
34

An independent study in our group has led to the synthesis of (*S*)-edulindiol (**35**) starting from (*R*)-3-hydroxy-2-methylpropionate (**Scheme 3**). The same substance was also obtained upon reduction of cathedulin K-19 with lithium aluminum hydride, and comparison of the two substances proved that the corresponding center in edulinic acid, and hence at C-9' of K-19, possess the (*S*) configuration.[22]



Scheme 3 *reagents and conditions* (i) $(MeO)_2PON_2$, *t*-BuOK, THF, (90%); (ii) Methyl 2-chloronicotinate, $(Ph_3P)_2PdCl_2$, CuI, Et_2NH, (61%); (iii) 5% HF/CH_3CN (100%); (iv) H_2, Lindlar cat. MeOH, (76%); (vi) $LiAlH_4$, THF-Et_2O (28%)

Little is known about the pharmacological activity of the cathedulin alkaloids. However, Kubo et al.[23] has reisolated cathedulins E-3, E-4, and E-5 and reports that all three compounds exhibit growth inhibitory activity against the pink bollworm at approximately 1 ppm. This activity is nearly as potent as that of azadirachtin (**36**),[24] which is one of the most effective naturally occurring insect growth inhibitors known.



Azadirachtin (**36**)

In addition to the cathedulins, several structurally related alkaloids based on euonyminol have been isolated from a number of different species in the family Celastraceae (**Figure 2**). Most of these natural products occur as a monomacrocyclic dilactone formed from acylation of the C-3 and C-12 hydroxyl groups of euonyminol with evoninic (**14**), wilfordic (**39**), or hydroxywilfordic acid (**40**). The remaining hydroxyl groups are esterified with 3-furoic (**37**), benzoic, acetic, nicotinic, and rarely by 5-carboxy-N-methylpyridonic acid (**38**). Although the gross structures of wilfordic and hydroxywilfordic acids have been known for more than 20 years, the absolute stereogenicity at C-9 of these acids is still undetermined.

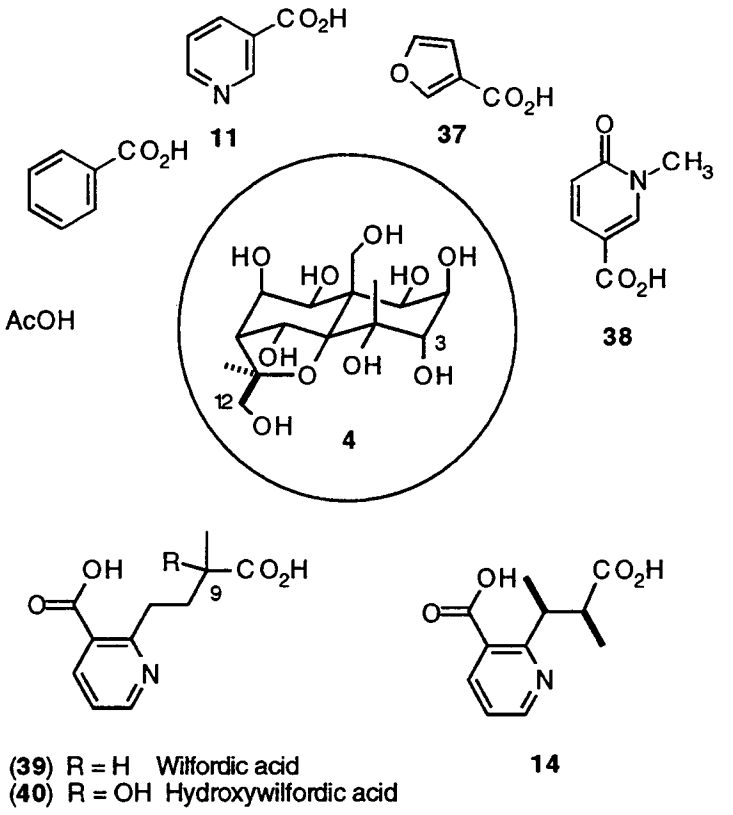
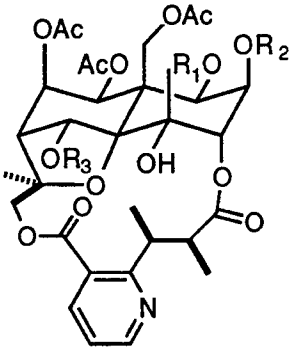


Figure 2: Esterifying Acids of Euonyminol of Celastraceaeous Alkaloids.

Isolation of this class of alkaloids from *Euonymus sieboldiana* was first announced by Yamada *et al.* in 1971.[25] The Yamada group elucidated the structure of euonymine (**41**) and neoeuonymine (**42**) and showed that they are based on a macrocyclic dilactone structure containing evoninic acid and euonyminol (**Table 1**). In 1986 Sousa isolated and established the structure of meyteine (**48**)[26] from *Maytenus guianensis.* This alkaloid is closely related to euonymine, different only with respect to esterification at the C-1 hydroxyl group. Subsequently, the isolation and structure determination of forrestine (**49**) from the root bark of *Tripterygium forrestii* was described by Jikai *et al.*[27] Recently, five new alkaloids, euojaponine A (**43**), C (**44**), I (**45**), L (**46**), and M (**47**), were isolated from the root bark of *Euonymus japonica*.[28] Euojaponine I,

L, and M are characterized by the presence of a nicotinyl ester at the C-1 hydroxyl group.

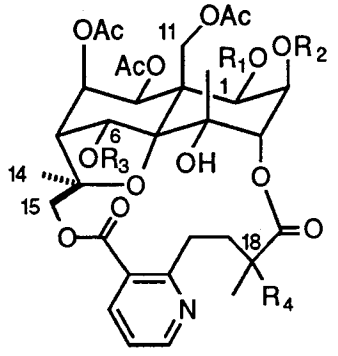


	R_1	R_2	R_3
Euonymine (**41**)	Ac	Ac	Ac
Neoeuonymine (**42**)	Ac	Ac	H
Euojaponine A (**43**)	COPh	Ac	H
Euojaponine C (**44**)	COPh	H	COPh
Euojaponine I (**45**)	nicotinyl	Ac	Ac
Euojaponine L (**46**)	nicotinyl	H	COPh
Euojaponine M (**47**)	nicotinyl	H	Ac
Mayteine (**48**)	COPh	Ac	Ac
Forrestine (**49**)	Ac	COPh	Ac

Table 1. Celastraceaeous Alkaloids Based on Euonyminol and Evoninic acid

A number of alkaloids based on wilfordic and hydroxywilfordic acids (**Table 2**), including wilfordine (**51**), wilforine (**52**), wilforzine (**55**), wilforgine (**54**), and wilfortrine (**53**), were isolated from *T. wilfordii* by Beroza.[29] The thunder god vine, *Tripterygium wilfordii* Hook, is widely distributed in southern China and is commonly used as a contact insecticide in rural China. Although its structure was unknown at the time, wilfordine (**51**) was an established antifeedant principle of *T. wilfordii* as early as 1950.[30] Recently an Italian group

has reexamined its strong antifeedant activity in detail.[31] The structure of wilfordine[32] was elucidated by Yamada, and the structures of wilforine and wilfortrine which were postulated by Smith on the basis of Beroza's earlier research, were confirmed by Wu *et al.*[33] Recently, a Chinese group has reisolated these alkaloids from *T. wilfordii* and has confirmed the structure of



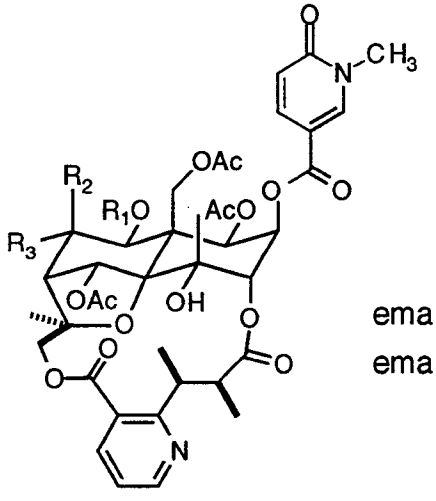
	R_1	R_2	R_3	R_4
wilfordine (**51**)	Ac	COPh	Ac	OH
wilforine (**52**)	Ac	COPh	Ac	H
wilfortrine (**53**)	Ac	3-furanoyl	Ac	OH
wilforgine (**54**)	Ac	3-furanoyl	Ac	H
wilforzine (**55**)	Ac	COPh	H	H
wilformine (**56**)	Ac	Ac	Ac	H
wilforidine (**57**)	Ac	H	Ac	OH
1-desacetylwilfordine (**58**)	H	COPh	Ac	OH
1-desacetylwilfortrine (**59**)	H	3-furanoyl	Ac	OH
2-debenzoyl-2-nicotinylwilforine (**60**)	Ac	nicotinyl	Ac	H

Table 2. Celastaceaeous Alkaloids Based on Euonyminol and Wilfordic, or Hydroxywilfordic acid.

wilforgine (**54**) postulated earlier by Smith, as well as that of wilforzine (**55**).[34] An alkaloid designated wilformine (**56**) was found to be identical with euonine[35]

previously isolated from *Euonymus sieboldiana*. Li *et al.* have established the structure of a new alkaloid wilforidine (**57**),[36] and in 1990 three additionalalkaloids from *T. wilfordii* were reported by the same group. These were shown to be 1-desacetylwilfordine (**58**), 1-desacetylwilfortrine (**59**), and 2-debenzoyl-2-nicotinylwilforine (**60**).[37]

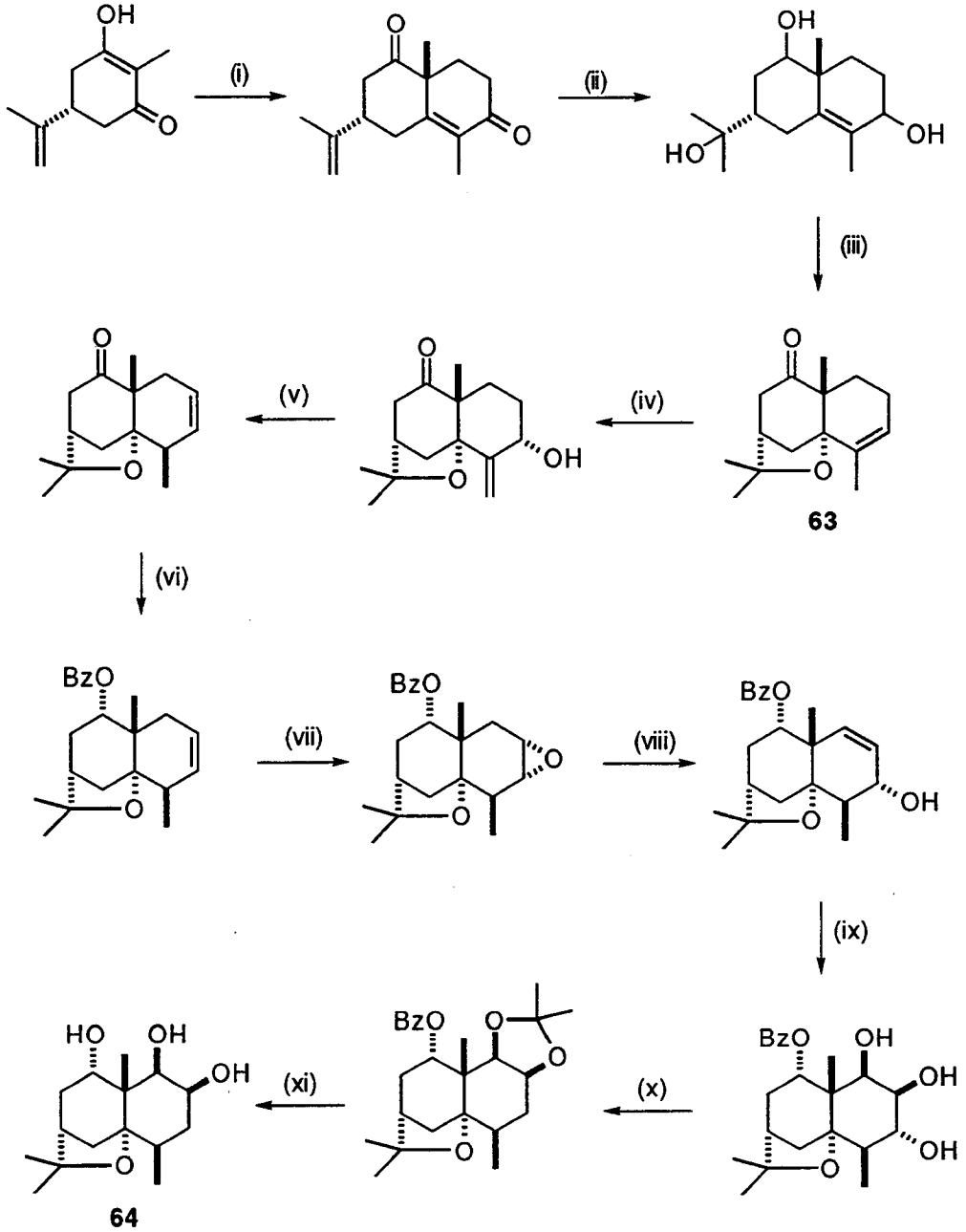
In 1989 emarginatine A (**61**),[38] a novel cytotoxic pyridone alkaloid was isolated from *Maytenus emarginata* and its structure was elucidated by means of spectroscopic analysis in conjunction with a single-crystal X-ray analysis. This compound is the first example of an euonyminol based alkaloid bearing a 5-carboxy-N-methylpyridonyl substituent. It showed strong *in vitro* cytotoxicity against KB cells (ED = 4.0 μg/mL). Subsequently, emarginatine B (**62**) based on the isoeuonyminol core was isolated from the same species and was found to exhibit more potent cytotoxicity against human KB cells (ED = 0.4 μg/mL)than emarginatine A.[39]



	R_1	R_2	R_3
emarginatine A (**61**)	OAc	OAc	H
emarginatine B (**62**)	COPh	H	OAc

No synthetic work on the sesquiterpene cores of the cathedulin alkaloids has been published. However, progress has been made toward the synthesis

of structurally more simple dihydroagarofuran derivatives which is relevant to the synthesis of euonyminol. In particular, the synthesis of isocelorbicol (**64**)[40]

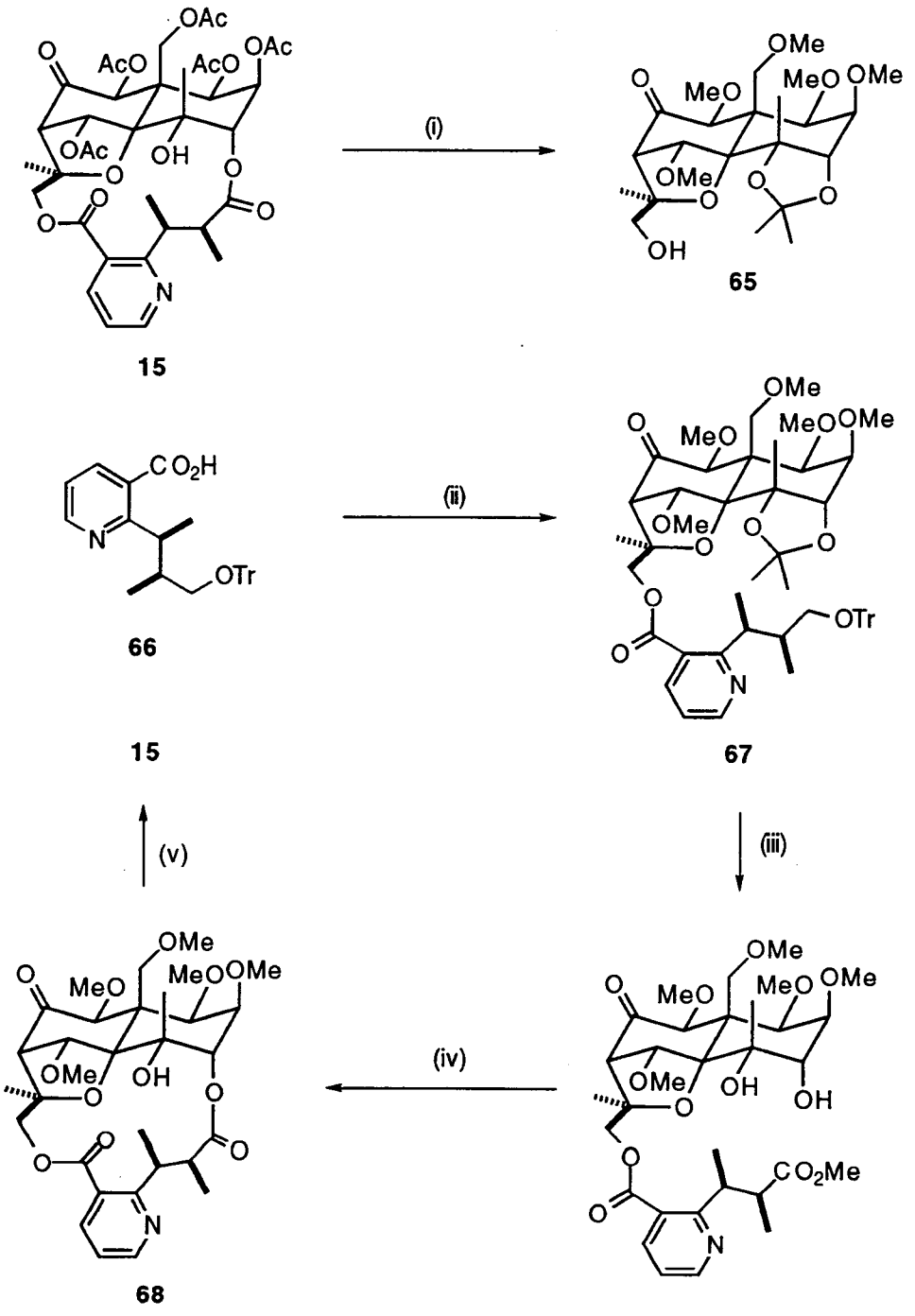


Scheme 4 *reagents and conditions* (i) ethyl vinyl ketone, NaOMe, then $(CO_2H)_2$; (ii) *m*-CPBA, then $LiAlH_4$; (iii) Jones' oxidation (overall 10%) (iv) *m*-CPBA, CH_2Cl_2, then LDA; (v) HN=NH, then $POCl_3$, py.; (vi) $LiAlH_4$, then *n*-BuLi, PhCOCl; (vii) *m*-CPBA; (viii) $(PhSe)_2/NaBH_4$ /EtOH, then *m*-CPBA / Et_2NH; (ix) OsO_4/py.; (x) acetonide formation, then Barton deoxygenation; (xi) $Ba(OH)_2$, then H^+

by Huffman describes highly regio- and stereoselective methodology for the introduction of hydroxyl functionality into the intermediate **63** (**Scheme 4**). The chemistry developed in the course of this work provides useful precedent for the elaboration of the multiple hydroxyl functionality present in this class of compounds.

Precedent for the construction of the macrocyclic dilactone moiety of the Celastraceaeous alkaloids from euonyminol and the corresponding pyridinedicarboxylic acid can be found in Yamada's synthesis of evonine (**15**)(**Scheme 5**).[41] In this work, the acid **66**, prepared from **15** by a series of degradation processes, was transformed to an activated mixed anhydride by treatment with ethyl chloroformate and triethylamine and was condensed with evoninol pentamethyl ether acetonide **65** to give the ester **67**. The latter was detritylated, and the exposed primary alcohol group was oxidized to a carboxylic acid. Removal of acetonide, methylation of the carboxylic acid, and subsequent cyclization afforded the dilactone **68** under somewhat unusual conditions (NaH, DMF) in 12% yield. Deprotection and acetylation then produced evonine (**15**).

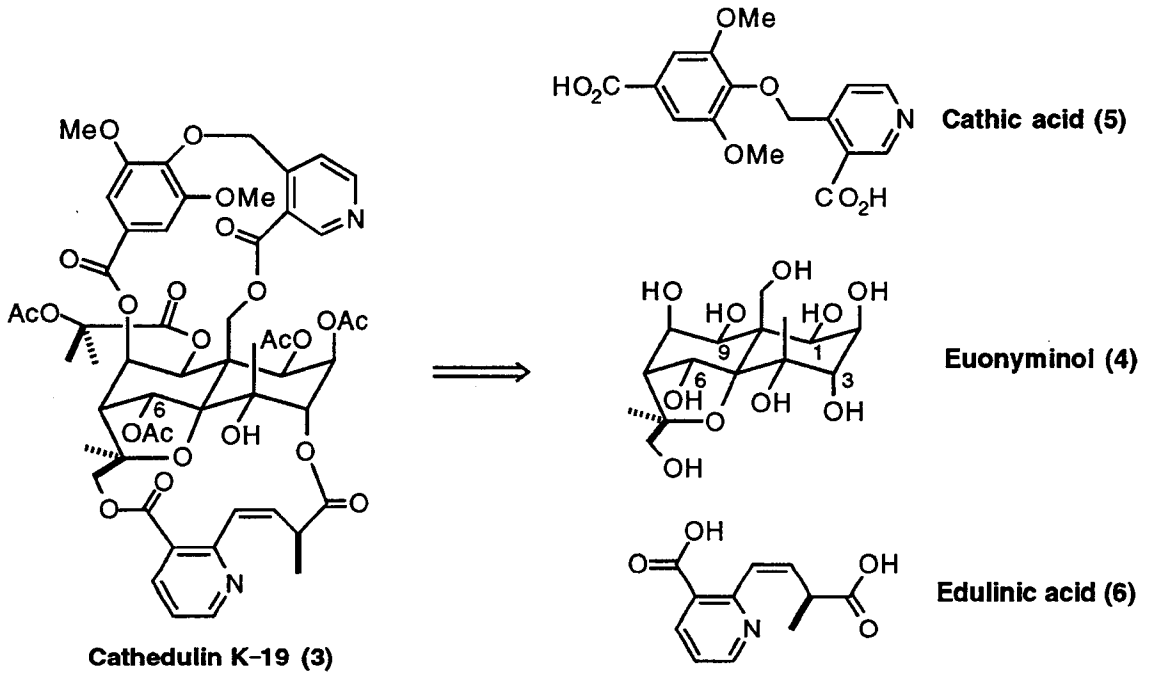
Our attention was focused on the synthesis of the two major fragments of cathedulin K-19, euonyminol (**4**) and dimethyl cathate (**69**). A concise and general synthetic entry to euonyminol could also provide a platform for the synthesis of other alkaloids described earlier. The present approach represents a racemic synthetic entry into euonyminol, however an asymmetric synthesis could be designed on the basis of the experience gained in the racemic series.



Scheme 5 *reagents and conditions* (i) a. NaOMe/MeOH, 5 °C; b. MeI, NaH, DMF; c. NaOMe/MeOH, RT; d. 2,2-dimethoxypropane, H^+; (ii) ethyl chloroformate, Et_3N, then **65**, DMAP, Et_3N, 90 °C (36%); (iii) a. 80% AcOH, 50 °C; b. CrO_3-py, 60 °C (70%); c. 50% AcOH, 85 °C (68%); d. CH_2N_2; (iv) a. NaH, DMF, RT (12%); (v) a. BCl_3, CH_2Cl_2; b. Ac_2O, py (35%).

Results and Discussion

By retrosynthetic analysis (**Scheme 6**) K-19[5] (**3**) can be divided into three major fragments. One fragment is the highly oxygenated sesquiterpene unit, euonyminol (**4**), and the other fragments are two dicarboxylic acids. These acids, named cathic (**5**) and edulinic acid (**6**) form macrolactones by attachment to euonyminol. This section is concerned with a straightforward synthesis of dimethyl cathate and a synthetic approach towards the complex structure of euonyminol (**4**).

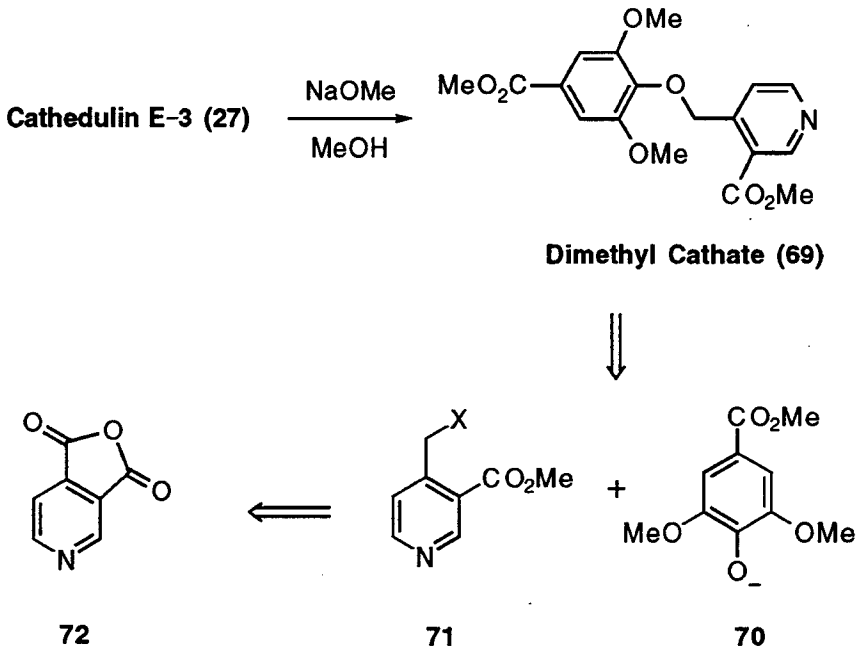


Scheme 6

Synthesis of Dimethyl Cathate

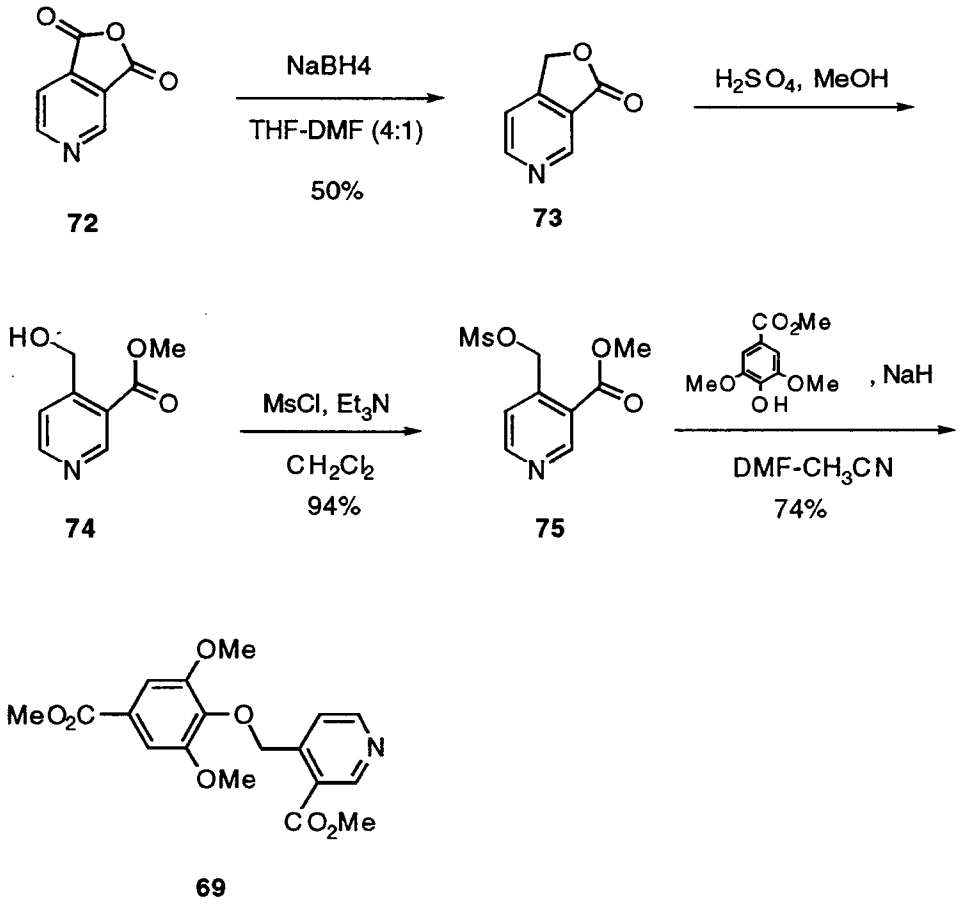
The synthesis of dimethyl cathate (**69**), a known degradation product from basic methanolysis of cathedulin E-3 (**27**),[20] was envisioned via a Williamson's coupling reaction of methyl syringate anion (**70**) and the nicotinic acid derivative

(**71**). The latter would be prepared from commercially available pyridine-3,4-dicarboxylic acid (**72**).



Scheme 7

Lactone **73** was obtained from pyridine-3,4-dicarboxylic acid anhydride (**10**) in 50% yield following a known procedure (**Scheme 8**).[42] Methanolysis of lactone **73** gave a 1:1 mixture of hydroxyl ester **74** and recovered starting material. Since **74** was prone to relactonization on silica gel, the crude mixture was treated with methanesulfonyl chloride to afford the unstable mesylate **75** along with recovered lactone **73** after column chromatography. Coupling of mesylate **75** and the sodium salt of methyl syringate gave dimethyl cathate **69**, with spectroscopic data (^{1}H NMR, ^{13}C NMR, MS, and mp) identical with the reported values.[20]

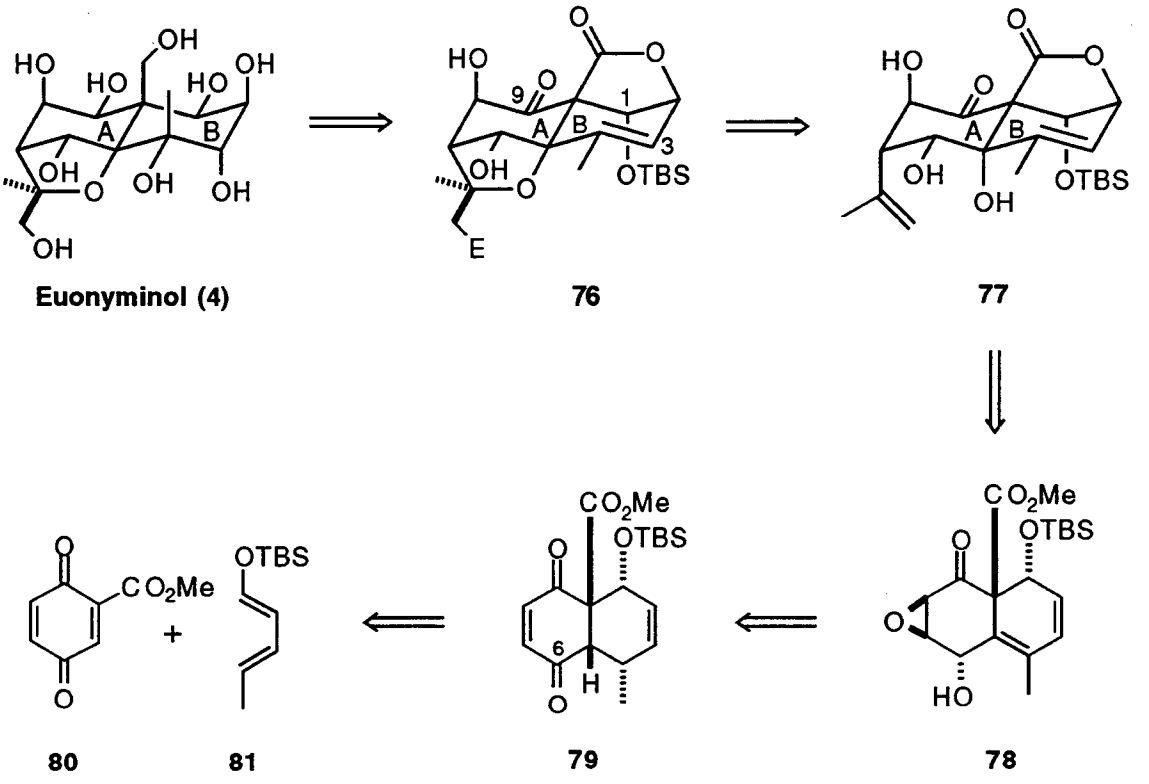


Scheme 8

A Synthetic Approach Toward Euonyminol (4)

Outlined is a retrosynthetic analysis of euonyminol (**Scheme 9**). Intermediate **76** would be transformed to euonyminol through a sequence of manipulations. These would include osmylation of the double bond at C-3, hydroxyl group inversion at C-1, and reduction of both the ketone and the lactone carbonyl group. It was envisioned that the tetrahydrofuran segment of **76** would be formed by an electrophilic cyclization of the angular hydroxyl group and the double bond of the axial isopropenyl group of **77**. Introduction of the axial isopropenyl group of **77** would be achieved via a diaxial opening of the epoxide of **78** using a cuprate reagent. The functionality of the B ring portion of

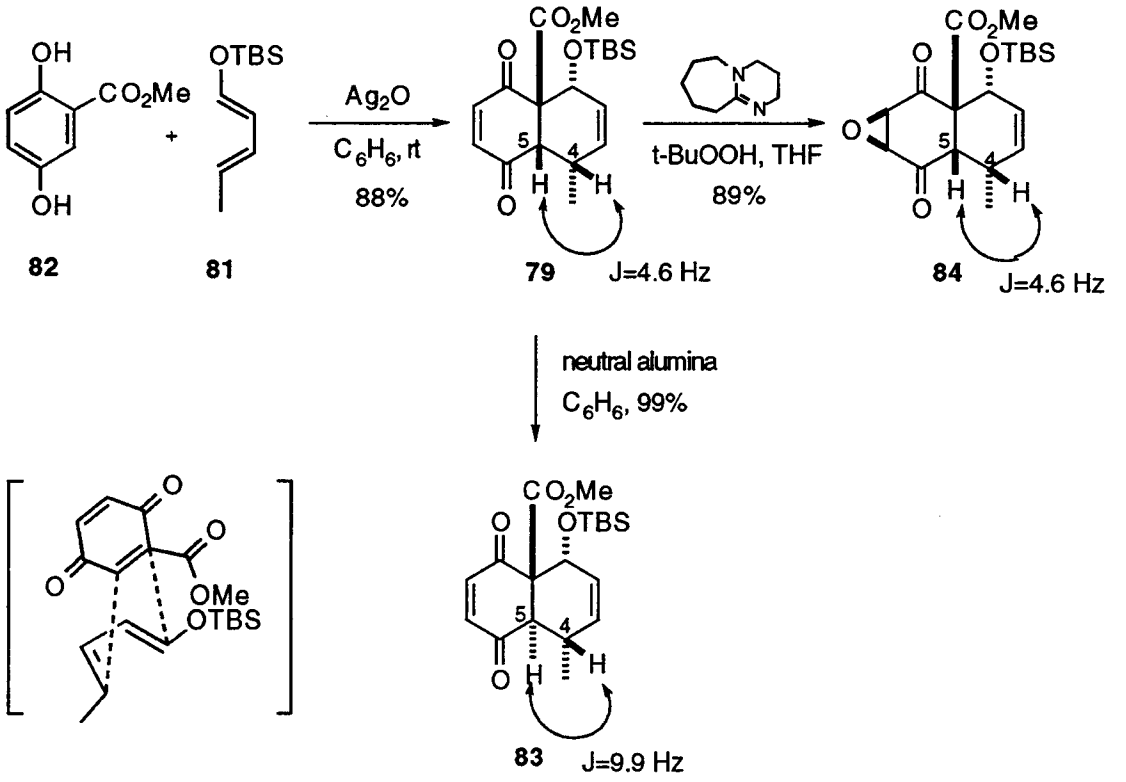
77 would be available from the diene segment of **78** via an oxidation reaction with singlet oxygen or epoxidation. Epoxide **78** would be available from **79** via a sequence of reactions: nucleophilic epoxidation of the electron deficient double bond at C-7, introduction of the homodiene moiety, and subsequent reduction of the ketone at C-6. An appropriate route to **79** would be a Diels-Alder reaction of the activated dienophile carbomethoxybezoquinone (**80**) and 1-*t*-butyldimethylsilyloxypenta-1,3-diene (**81**).



Scheme 9

The route to euonyminol began with a Diels-Alder reaction[43] of carbomethoxybenzoquinone (**80**), generated *in situ* from hydroquinone **82**, with 4 equivalents of an isomeric mixture of 1-*t*-butyldimethylsilyloxypenta-1,3-diene . The latter was prepared from 2-pentenal by treatment with *t*-butyldimethylsilyl triflate in the presence of triethylamine.[44] A single stereoisomer **79** was

obtained in high yield from the Diels-Alder reaction, reflecting a kinetic resolution among the (E, E)-diene and the other isomers since the dienes were a mixture

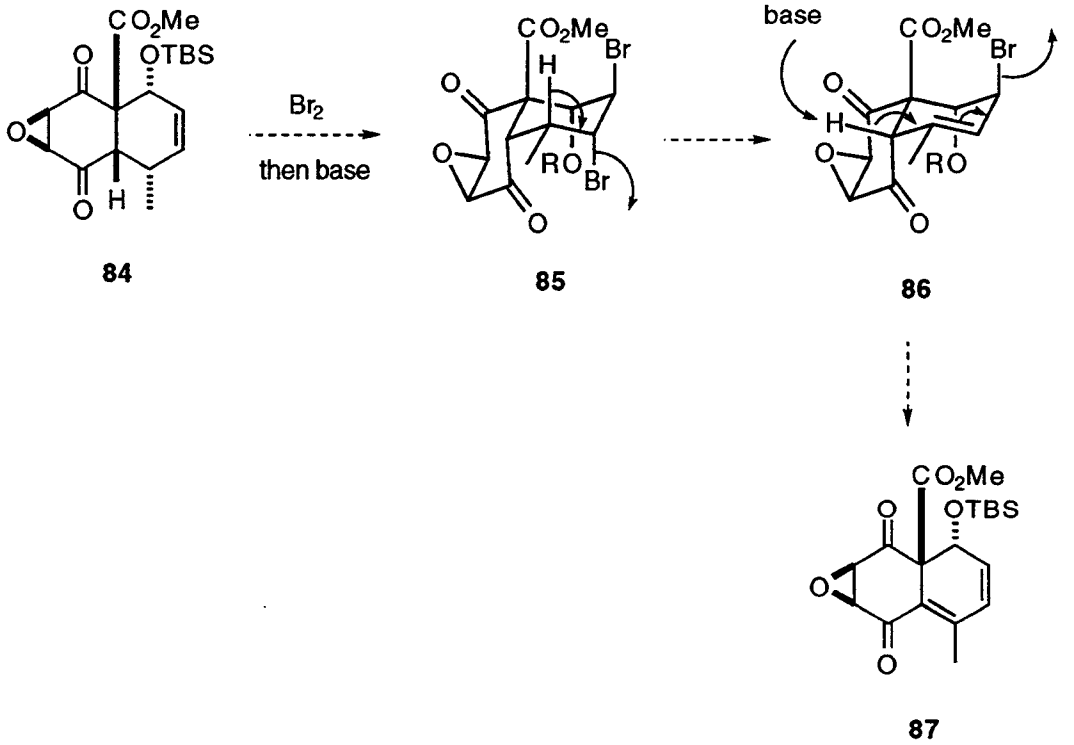


Scheme 10

of all four isomers containing 25 to 30% of the (E, E)-diene **81**. The stereochemical outcome of the Diels-Alder reaction was deduced from the coupling constant (J=4.6 Hz) between H-4 and H-5 of enedione **79**, which supported an axial-equatorial disposition of these two protons. The coupling constant of the same pair of protons (J=9.9 Hz) of the *trans* isomer **83**, obtained by treatment of **79** with neutral alumina, indicated an axial-axial relationship of H-4 and H-5. This result is consistent with *endo* addition[45] of the (E, E)-diene to the quinone as depicted in **Scheme 10**. Subsequent nucleophilic epoxidation[46] of **79** afforded the epoxide **84** stereoselectively in 90% yield. The β-configuration of the epoxide moiety of **84** was assigned based on steric[47]

considerations which dictated that attack of *t*-butylhydroperoxide should occur at the convex face of **79**. Since epimerization at C-5 of **79** is facile under mild basic conditions as observed, there was the possibility that epimerization occurred during the epoxidation reaction. However, analysis of the coupling constant (J=4.6 Hz) between H-4 and H-5 of **84** showed no sign of epimerization at the ring junction in this compound.

Initially introduction of the homodiene moiety of **87** was planned via bromination of the double bond of **84** and a sequence of elimination reactions using base i.e., *trans* 1,2-elimination of hydrogen bromide from **85** and subsequent 1,4-elimination of hydrogen bromide from **86**.

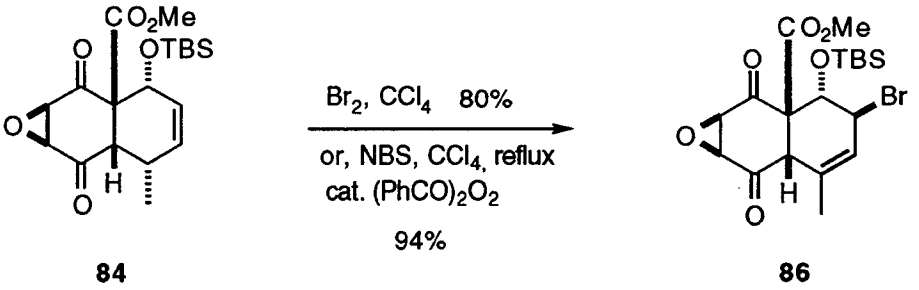


84 **85** **86** **87**

Scheme 11

Unexpectedly bromination of **84** using bromine in carbon tetrachloride afforded the allylic bromide **86** instead of the dibromide **85**. The stereochemisty

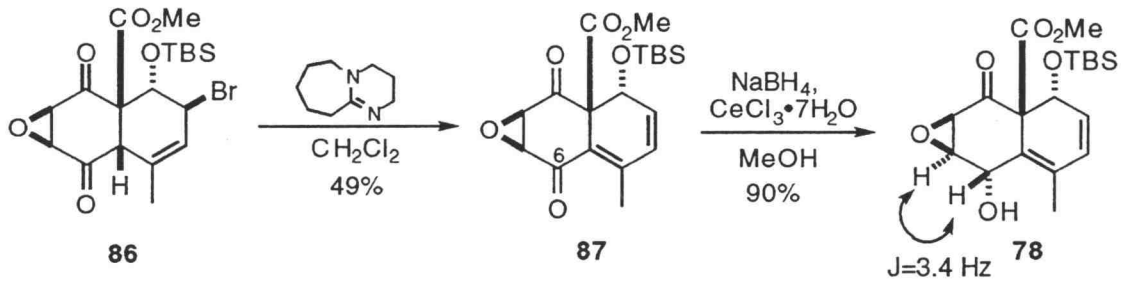
of the introduced bromide of **86** was assumed to be as shown on the basis of the well known diaxial opening of the intermediate bromonium ion[48] to form **85** and a subsequent *trans* elimination.[49] The same product could also be obtained by allylic bromination of **84** with N-bromosuccinimide[50] in the presence of a catalytic amount of benzoyl peroxide (**Scheme 12**).

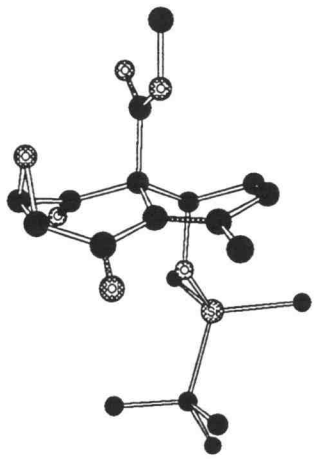


84 **86**

Scheme 12

A 1,4-elimination of hydrogen bromide from **86** using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[51] provided the homoannular diene **87**, and reduction of the latter under Luche conditions[52] gave **78** as a single isomer in a chemo- and steroselective manner (**Scheme 13**). The α configuration of the resultant hydroxyl group of **78** was rationalized based on steric considerations. Close examination of the MM2 energy minimized structure of **87** predicted that the A ring adopted a boat conformation making the top face of the ketone at C-6 more accessible to hydride attack. The chemoselectivity of the reduction of **87** in which the conjugate ketone group is reduced in preference to the saturated ketone group[53] is also an interesting result and is discussed below.



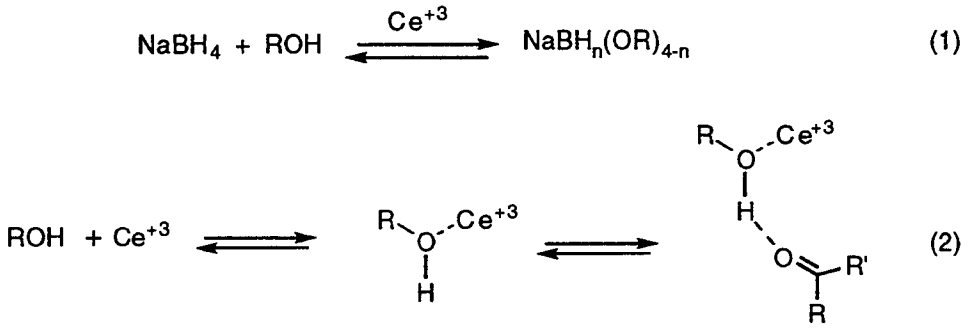


minimized structure **87**

Scheme 13

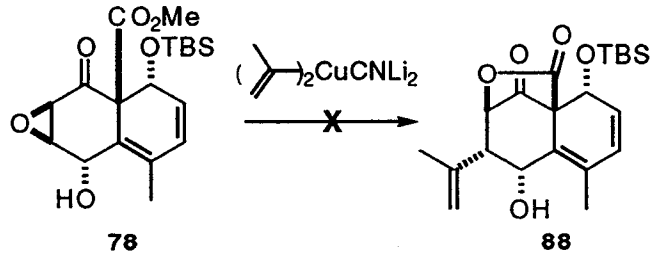
According to a mechanistic study by Luche and Gemal,[54] the major effect of ceric ion in the Luche reduction is catalysis of borohydride decomposition by the hydroxylic solvent to give a more reactive alkoxyborohydride (equation 1). In addition, the Lewis acidic ceric ion coordinates to the Lewis basic hydroxyl solvent, making the medium more acidic. The latter effect presumably accelerates reaction by a coordination of the Lewis acidic hydrogen of the hydroxylic solvent to the carbonyl group (equation 2). Since it is known that the Lewis basicity of an α, β-unsaturated ketone is greater than that of a saturated ketone,[55] the observed selectivity may be the result of a difference in the relative basicity between the two ketone groups. This would result in selective activation by the cerium (III) coordinated hydroxylic

solvent of the α, β-unsaturated ketone leading to more rapid attack at the C-6 carbonyl group of **87**.



Scheme 14

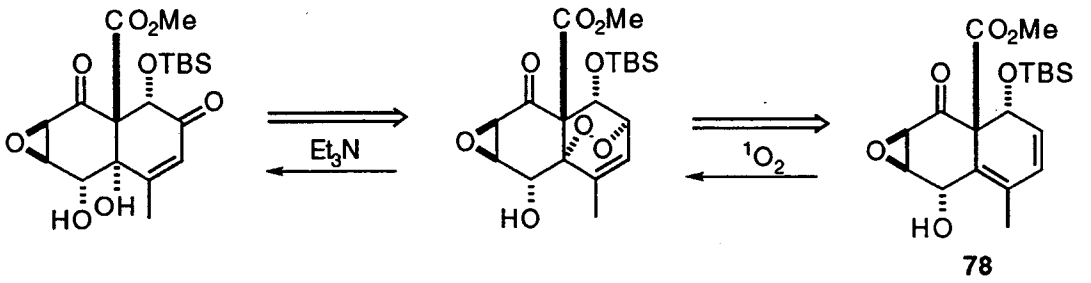
With this efficient route to **78** established, opening of the epoxide[56] was attempted with cuprate reagents under a variety of conditions. Our expectation was that opening of the epoxide and subsequent lactone formation would lead to **88**. However, all attempts to effect this transformation proved unsuccessful.



Scheme 15

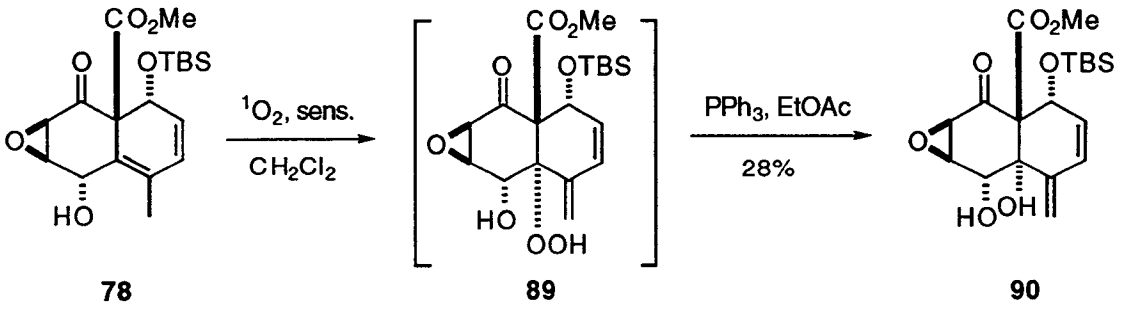
Functionalization of the diene moiety of **78** with singlet oxygen[57] was also examined as an entry to the B ring of euonyminol. It was hoped that singlet oxygen would undergo [4+2] cycloaddition with **78**. This transformation would not only introduce the angular hydroxyl group but would also generate a direct precursor of the B ring of **4**. We also hoped that the allylic hydroxyl group of **78** would direct the incoming dienophilic singlet oxygen *syn* to the hydroxyl group

(**Scheme 16**) since a recent detailed study of the directing effect of an allylic hydroxyl group on the ene and [4+2] cycloaddition reactions of singlet oxygen provides exellent precendence for this result.[58]



Scheme 16

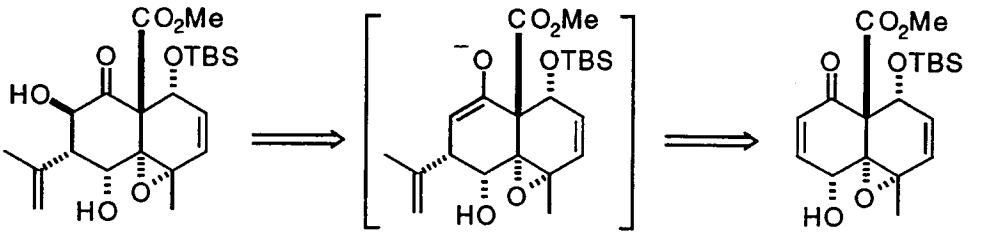
However, treatment of **78** with singlet oxygen afforded the ene product **90** after reduction of intermediate hydroperoxide **89** with triphenylphosphine rather than the desired endo peroxide resulting from [4+2] cycloaddition. The stereochemistry of **90** is based on an assumed hydroxyl group directing effect which would lead to a *cis* diol.



Scheme 17

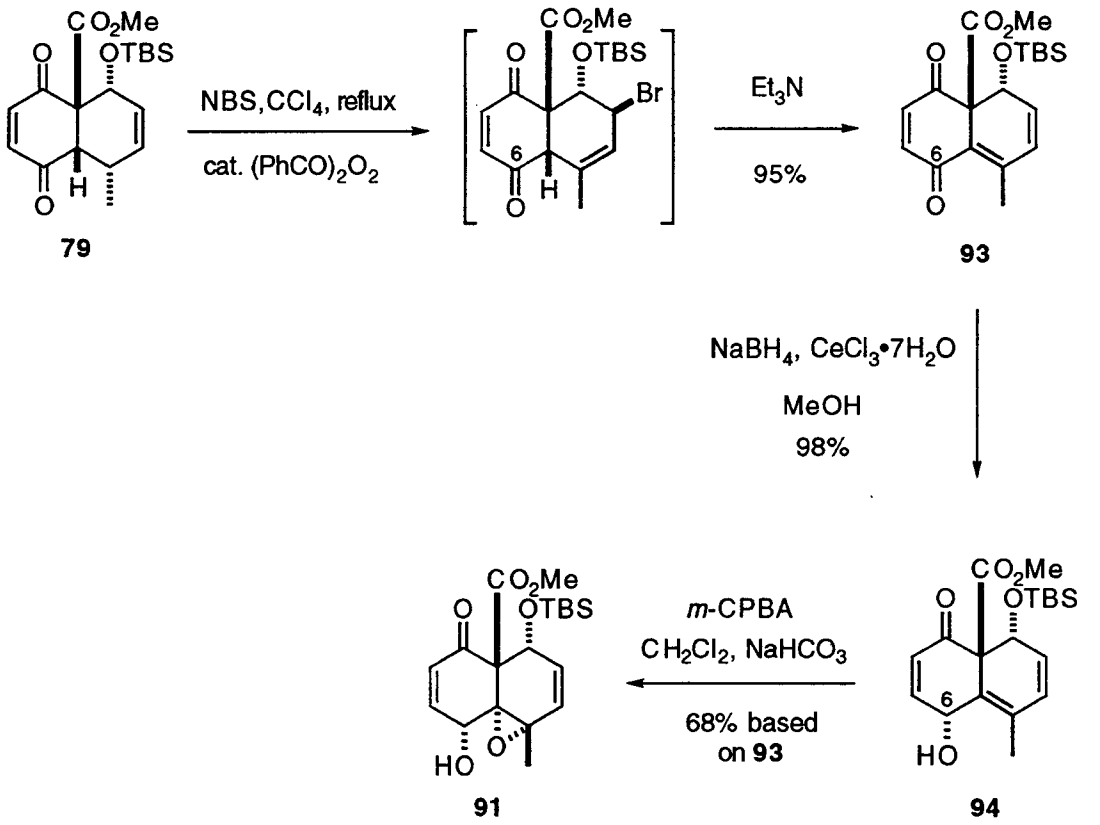
The inability to effect the epoxide opening of **78** with cuprate reagents prompted to turn our attention to an alternative route that would accomplish the same overall transformation (**Scheme 18**). This plan called for the preparation of epoxy enone **91**, which would be functionalized to yield **92** via a Michael

addition and subsequent capture of the intermediate enolate by a hydroxylating reagent.



Scheme 18

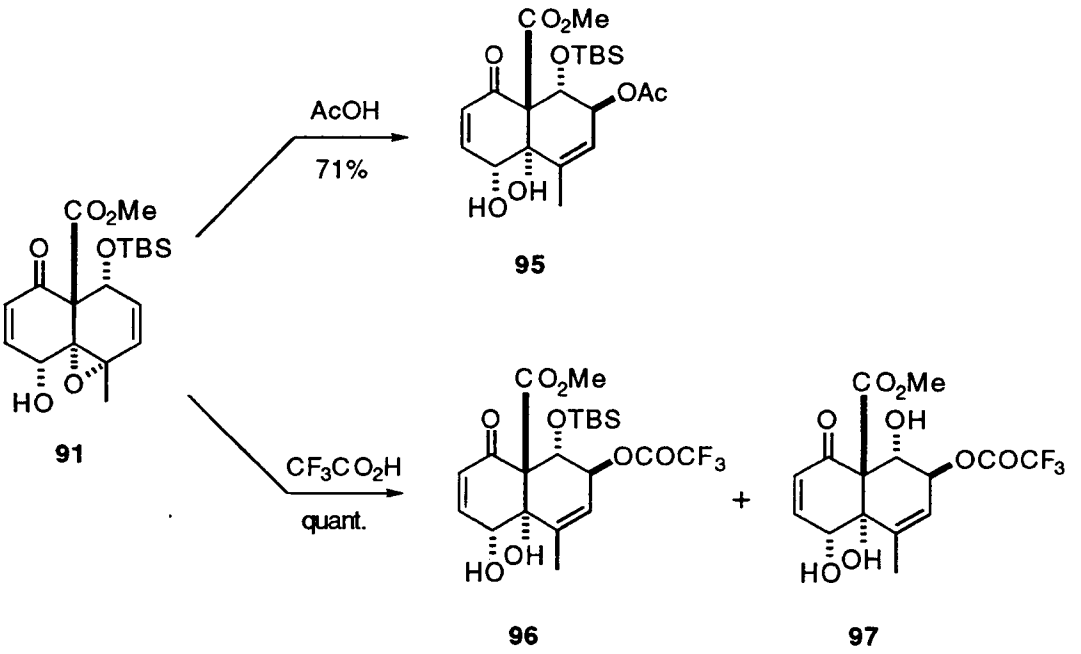
Allylic bromination of Diels-Alder adduct **79** with N-bromosuccinimide, followed by elimination of the unstable allylic bromide using triethylamine, afforded trienedione **93** in a single-pot operation (**Scheme 19**). Reduction of **93** with the Luche reagent[52] afforded γ-hydroxy enone **94** with complete regio- and stereoselectivity. The selective reduction of the C-6 ketone group of **93** can again be explained assuming greater basicity of the cross conjugated ketone group relative to the α, β-unsaturated ketone group as proposed for the reduction of **87**. However, there is no pertinent literature data for the relative basicities of these two ketone groups. A further interesting feature of the reduction of **93** is that a highly dilute solution of the reagents relative to the standard Luche reduction conditions and slow addition of sodium borohydride was found to be crucial for good yields. Subsequent epoxidation of **94** with *m* -chloroperbenzoic acid gave epoxy enone **91** as a single stereoisomer. This is a result of the directing influence of the 6α-hydroxyl substituent (Henbest effect)[59] on the epoxidation.



79 93 91 94

Scheme 19

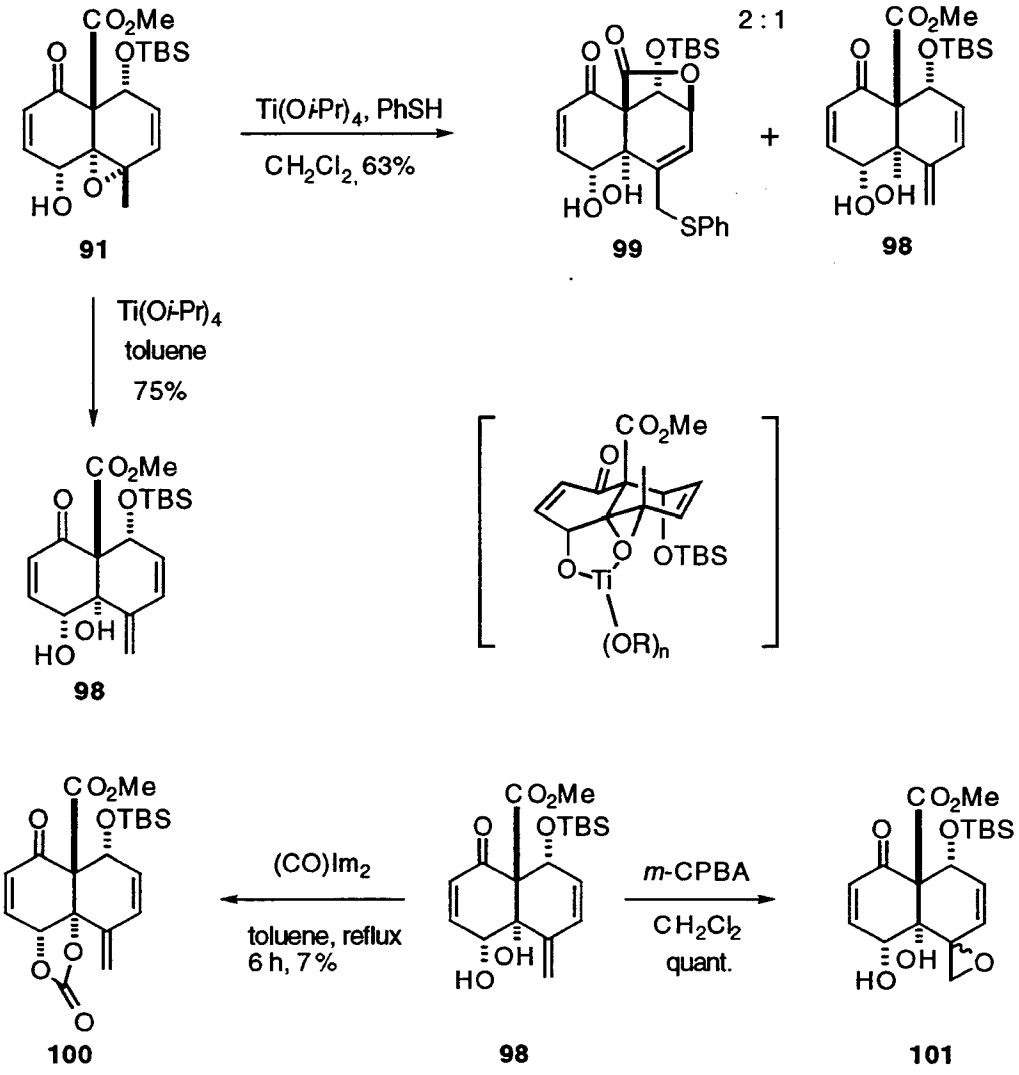
It was found that the vinyl epoxide functionality of **91** could be manipulated in a variety of ways. Thus, treatment of **91** with acetic acid at 60 °C for 4 h gave allylic acetate **95** which has much of the functionality required for the B ring of euonyminol. When the more acidic trifluoroacetic acid was used at room temperature for 2 h, trifluoroacetate **96** and its deprotected derivative **97** was obtained in a ratio of 1:2 (**Scheme 20**).



Scheme 20

When the hydroxy enone **91** was treated with titanium tetraisopropoxide, the conjugated diene **98** was obtained as a single product.[60] This transformation probably resulted from tertiary carbocation formation assisted by a hydroxyl-directed internal coordination of titanium tetraisopropoxide to the epoxide moiety as depicted in **Scheme 21**. This presumed activation of epoxide **91** by titanium tetraisopropoxide led us to examine the possibility of intercepting the tertiary carbocation intermediate with nucleophiles. Surprisingly, thiophenol led to the allyl sulfide **99** together with **98** in a ratio of 2:1. The mechanistic pathway for the formation of allyl sulfide **99** is not yet known. However, the independent conversion of **98** to **99** under the same reaction conditions implies that diene **98** is an intermediate. When benzoic acid was used in the reaction with **91**, **98** was formed exclusively. The formation of cyclic carbonate **100** from **98** by treatment with carbonyl diimidazole[61] confirmed the *cis* 1,2-diol relationship and thus established the *cis* relationship of the secondary hydroxyl

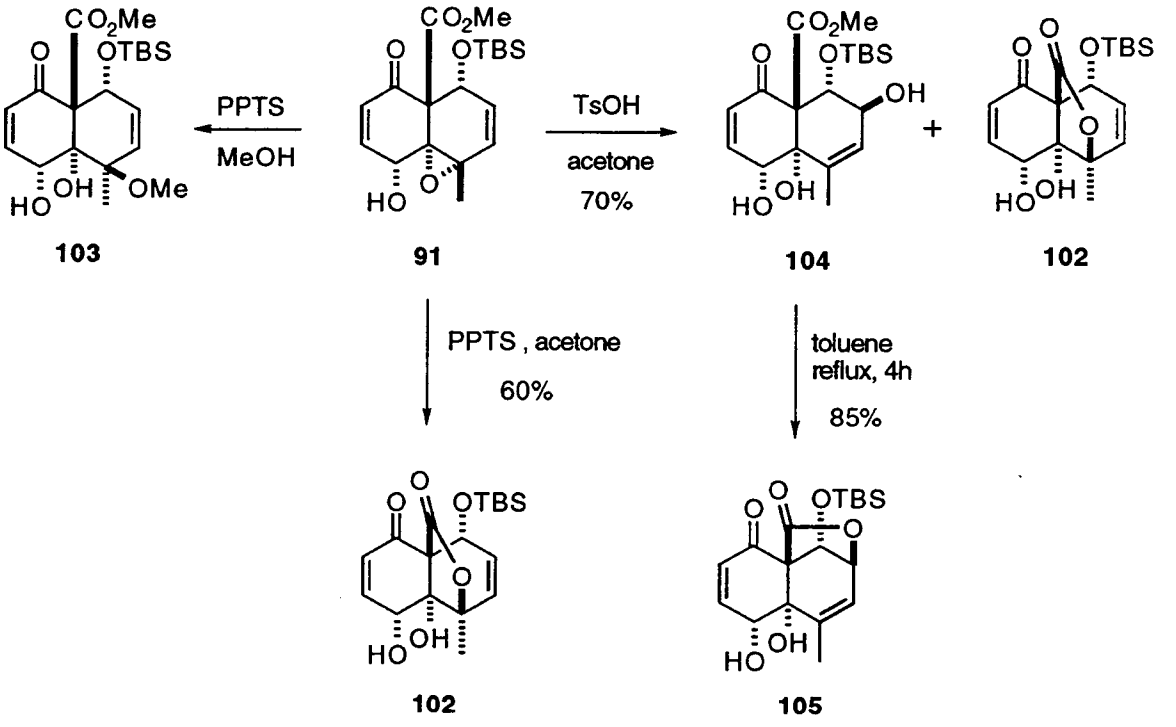
and epoxide group in **91**. Epoxidation of **98** with *m*-chloroperbenzoic acid afforded a 1:1 mixture of epoxides **101** which were not examined further due to the poor stereoselectivity. In principle, the α-epoxide from this reaction could afford a means of access to the B ring functionality of euonyminol but subsequent development with **101** was not appealing.



Scheme 21

Further exploration of the chemistry of **91** led to the discovery that lactone **102** was formed with pyridium *p*-toluenesulfonate in acetone. On the other

hand, when methanol was used as the solvent, the methyl ether **103** was obtained. This was transformed to **102** under prolonged exposure to these conditions. In less polar solvents such as methylene chloride, there was little reaction and most of the starting material was recovered. A combination of *p*-toluenesufonic acid in acetone with **91** produced a mixture of allylic alcohol **104** and lactone **102** in a ratio of 2:1. The alcohol **104** underwent lactionization to give **105** in refluxing toluene.(**Scheme 22**).

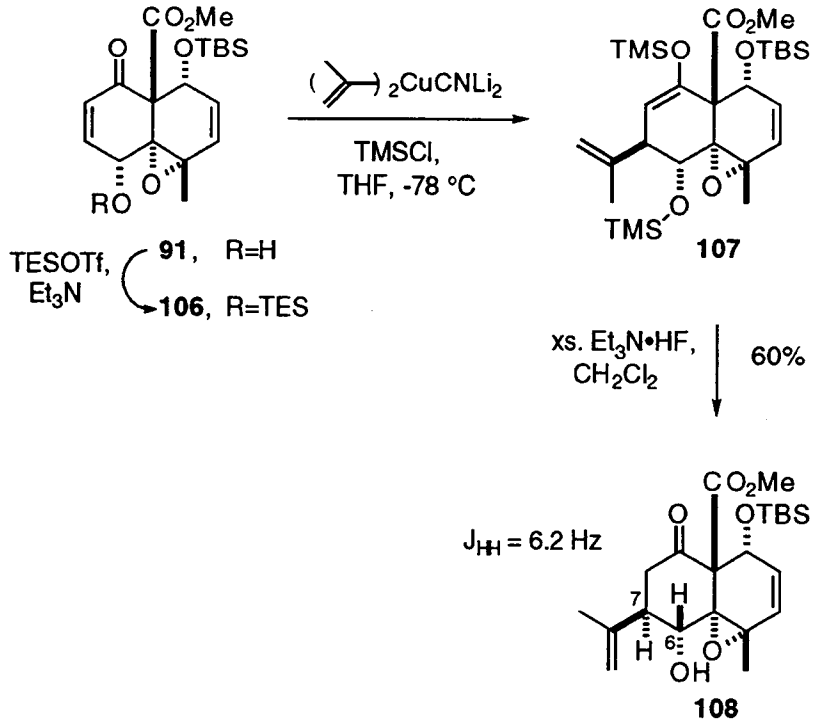


Scheme 22

In summary, the vinyl epoxide moiety of **91** was functionalized in various ways under mild acidic conditions. Acetic acid opened the vinyl epoxide moiety in an *anti* S_N2' fashion to give **95**. Similarly, trifluoroacetic acid afforded **96** and **97**. On the other hand, methanol attacked in an S_N2 fashion to form **103** in the presence of pyridinium *p*-toluenesulfonate. In the absence of an external nucleophile the participation of the angular ester group was observed to form

102. Hydroxyl directed internal coordination of epoxide of **91** by titanium tetraisopropoxide afforded diene **98**. Unexpectedly, sulfide **99** was obtained in the presence of thiophenol.

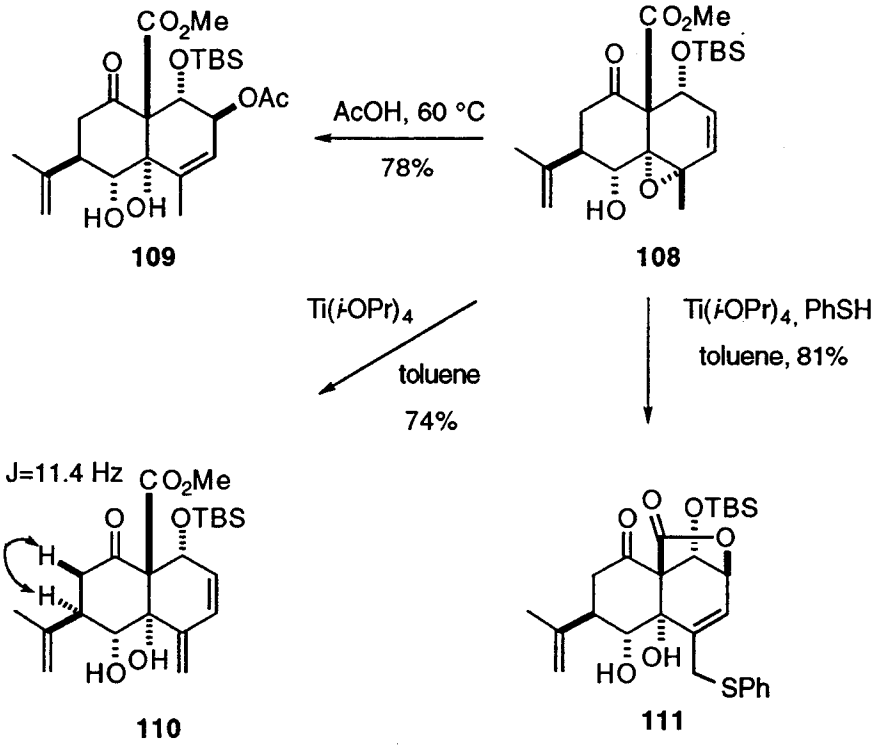
Having acquired a good understanding of the reactivity of the epoxide **91**, we next turned our attention towards introduction of the requisite three-carbon unit into ring A. Initially, cuprate addition to the enone moiety of **91** was envisioned for this purpose. Unfortunately, addition to **91** could not be accomplished with the higher order isopropenyl cuprate reagent. Nor was the protected enone **106** responsive to the cuprate reagent in the presence of boron trifluoride etherate. However, isopropenyl cuprate added smoothly to the enone of **91** in the presence of trimethylsilyl chloride (TMSCl)[62] to yield the enol ether **107** in which the C-6 alcohol had also been silylated. (**Scheme 23**). An initial attempt to remove the two trimethylsilyl groups of **107** by acidic hydrolysis failed and instead gave an unidentified product. However, this conversion was accomplished cleanly following Rubottom's procedure[63] using the triethylamine-hydrofluoric acid complex[64] in methylene chloride and afforded isopropenyl ketone **108** in good yield.



Scheme 23

The configuration of the isopropenyl substituent of **108** was not clear from the available NMR data. In particular, the coupling constant (J=6.2 Hz) between H-6 and H-7 represents a value which is intermediate between axial-axial (J=11-15 Hz) and axial-equatorial coupling constants (J=2-6 Hz) for vicinal protons of a cyclohexane in a chair conformation. However, even though the stereochemical outcome of conjugate addition to **91** was uncertain, further functionalization of the epoxide moiety was attempted with **108** in the same way as for **91** (**Scheme 24**). Thus, treatment of **108** with acetic acid at 60 °C afforded the allylic acetate **109** and with titanium tetraisopropoxide, **108** gave diene **110.** The coupling constant (J=12.4 Hz) between H-6 and H-7 of **110** showed a value typical of diaxial protons indicating β-configuration of the isopropenyl group. When **108** was treated with titanium tetraisopropoxide and thiophenol at -5 °C for 15 days, the allylic sulfide **111** was obtained in good yield

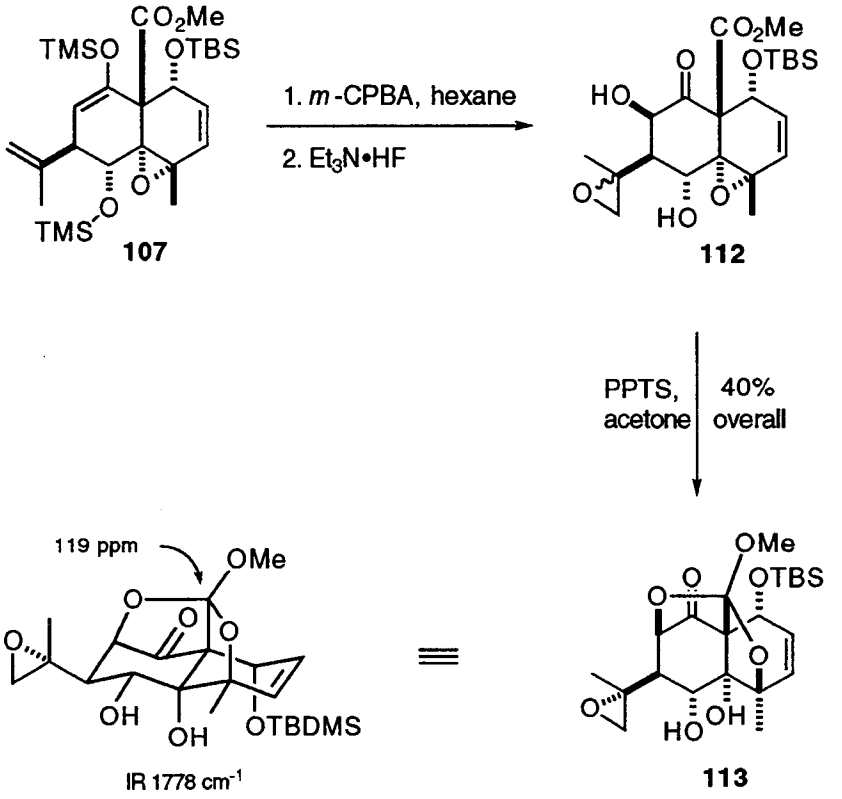
which similarly gave evidence for the undesired β configuration of the isopropenyl substituent. Although these results seemed discouraging from the perspective of an approach to euonyminol, it was decided to investigate the chemical properties of **107** in order to gain experience in manipulating functionality in this structure.



Scheme 24

Exposure of enol ether **107** to *m*-chloroperbenzoic acid, followed by treatment with triethylamine-hydrofluoric acid complex, gave epoxy diol **112** as a 3:1 mixture of stereoisomers at the epoxide (**Scheme 25**). Subsequent treatment of **112** with pyridinium *p*-toluenesulfonate in acetone afforded orthoester admixed with its epoxide isomer in the same 3:1 ratio. The major isomer **113** was purified and showed a ^{13}C NMR resonance for the orthoester carbon at 118 ppm and a ketone carbonyl frequency at 1779 cm^{-1} consistent

with an alkoxy substituent adjacent to a carbonyl contained in a 5-membered ring. Finally, an X-ray analysis of crystalline **113** confirmed the structure shown and proved unambiguously that the isopropenyl group occupied the undesired equatorial (β) position (**Figure 3**). Thus, our assumption that a cuprate reagent would attack the enone moiety of **91** from the axial (α) direction on stereoelectronic grounds[65] proved ill founded and the experimental result indicates that there is still much to be learned about this class of reactions. Possibly, the α orientation of the γ-hydroxyl substituent[66] of **91** interferes with delivery of the isopropenyl group or perhaps the mechanism[67] is more complex than we envision.



Scheme 25

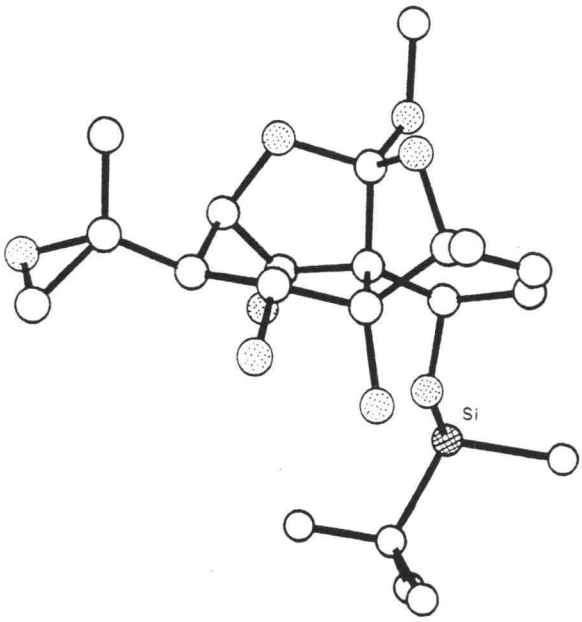
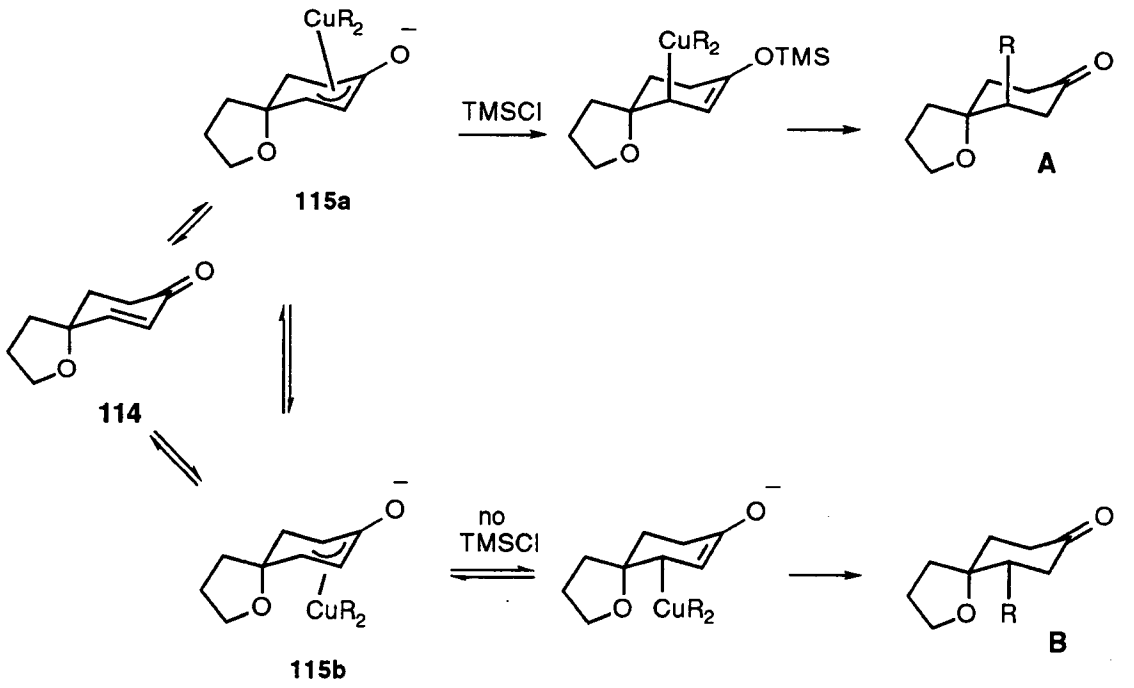


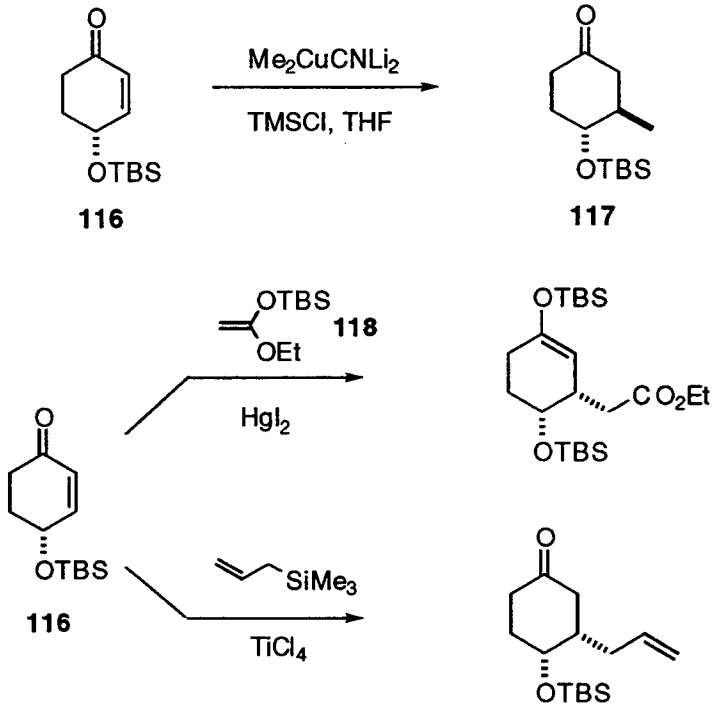
Figure 3: Pluto Diagram from X-ray Analysis of **113**

Two relevant studies on the stereochemical outcome of the conjugate addition to enones similar to **91** were found in the literature. In a study of the role of TMSCl in cuprate addition, Corey and Boaz reported on the basis of a ^1H NMR study that TMSCl and cuprates are mutually compatible from -78 °C to -50 °C and that the presence of TMSCl not only enhanced the rate of conjugate addition but also affected the stereoselectivity. The addition of dimethyl cuprate to the enone **114** showed a complete reversal of stereoselectivity in the presence (A:B=97:3), or absence (A:B=8:92) of TMSCl as shown in **Scheme 26**. They speculated from these results that the specific action of TMSCl was the capture of a (β)-η^3-d,π^*-complex **115a** which could equilibrate with the thermodynamically more stable (α)-η^3-d,π^*-complex **115b** in the absence of TMSCl. The exclusive attack *anti* to the γ-oxygen group in the presence of TMSCl was thought to be a result of the interaction of the σ^* orbital of the C-O

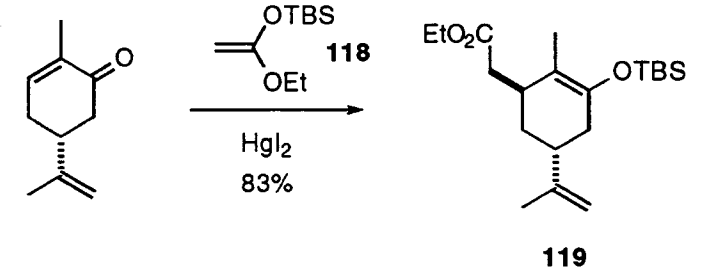


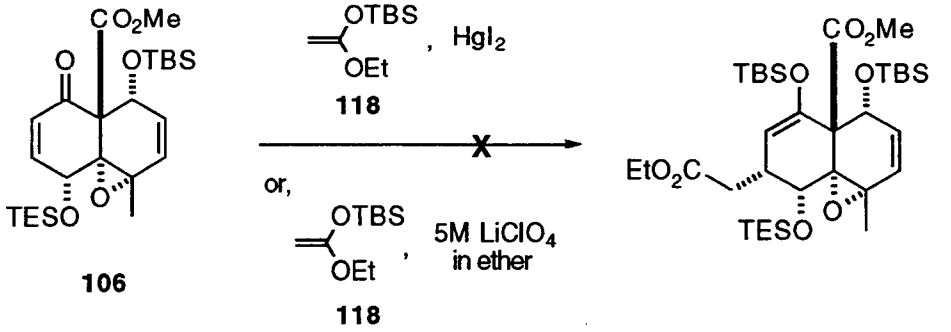
Scheme 26

bond with the (β)-η^3-d,π^*-complex **115a** hyperconjugatively. Consistent with Corey's proposal, Danishefsky and coworkers[68] reported that lithium dimethylcuprate added in an *anti* fashion to the γ-silyloxy group of **116** to give **117** exclusively in the presence of TMSCl. Danishefsky also found that Lewis acid-catalyzed 1,4-addition of silylketene acetal **118** to **116** showed a completely reversed stereoselectivity, resulting in a *syn* relationship with the silyloxy group in constrast to *anti* attack observed with cuprate reagent (**Scheme 27**). Trimethylallylsilane also added *syn* to the silyloxy group of **116** under titanium tetrachloride catalysis.



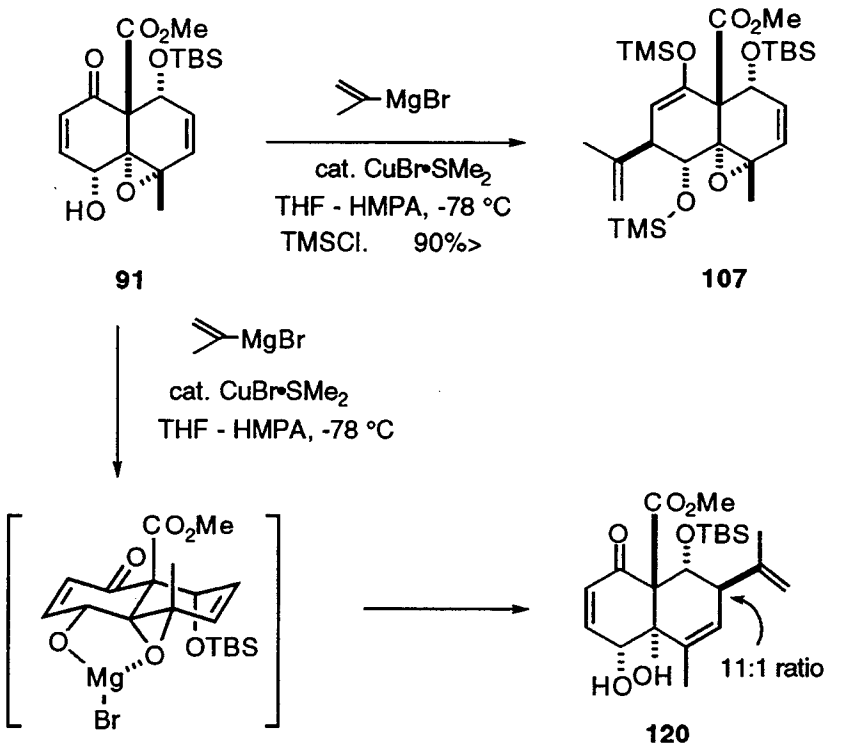
Scheme 27





Scheme 28

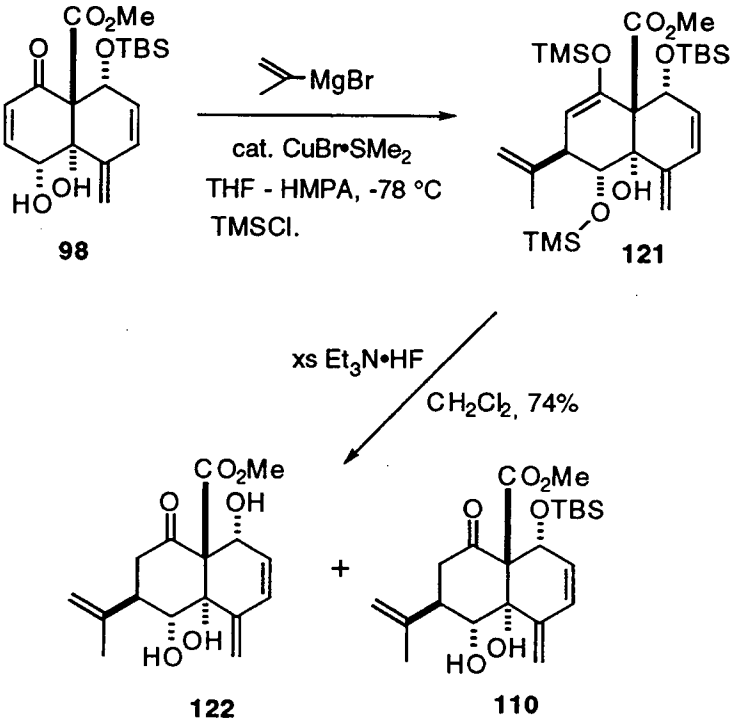
With these data in mind, various Lewis acid-catalyzed 1,4-additions to **106** were attempted (**Scheme 28**). First, however, it was ascertained through a model study that silylketene acetal **118** added smoothly to (*R*)-carvone to form the silylenol ether **119** as a single isomer in 83% yield. However, most of the reactant was recovered when the same conditions were applied to the enone **106**. Addition of **118** to **106** also proved unsuccessful with Grieco's procedure[69] using 5 M lithium perchlorate in diethyl ether as the reaction medium.



Scheme 29

There are several reports[70] indicating that the stereochemical outcome of cuprate addition to enones is dependent not only on the cuprate species but also on the solvent. To explore the effect of reaction parameters on the cuprate addition reaction, cuprous bromide dimethylsulfide complex[71] catalyzed conjugate addition of isopropenylmagnesium bromide to **91** was attempted

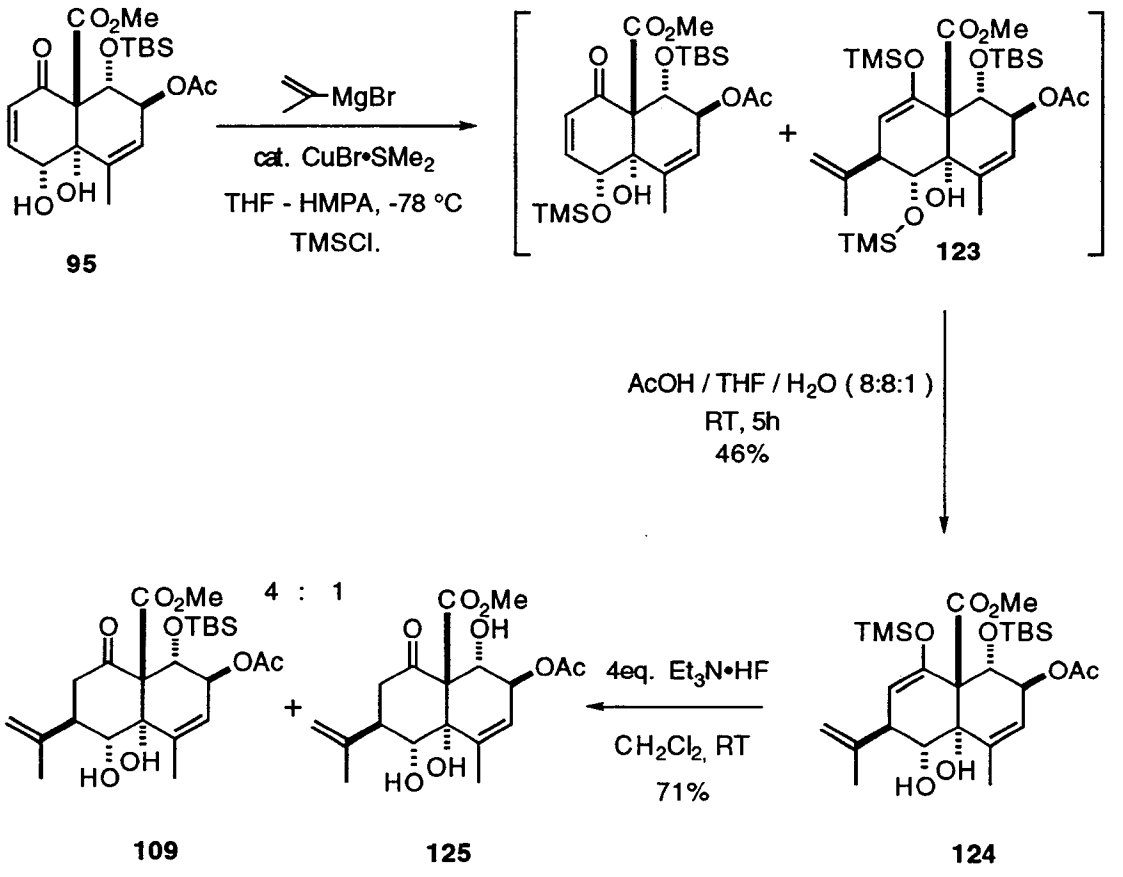
(**Scheme 29**). In the absence of TMSCl, the isopropenyl group added to the vinyl epoxide moiety in S_N2' fashion to form enone **120**, presumably via internal activation of the vinyl epoxide moiety of **91** by an alkoxymagnesium bromide species. On the other hand, in the presence of TMSCl[72] the β-adduct **107** was obtained as the sole product.



Scheme 30

The cuprous bromide-catalyzed addition of isopropenylmagnesium bromide was also examined with other enones including **98** (**Scheme 30**) and allylic acetate **95** (**Scheme 31**). Unfortunately, conjugate addition to **95** and **98** resulted in the formation of β-adducts exclusively as was observed with **91**. Conjugate addition proceeded smoothly with **98** to form enol ether **121** in high yield, but in the case of allylic acetate **95** the reaction did not go to completion even with excess Grignard reagent. Cleavage of the trimethylsilyl ether of **121** with triethylamine-hydrofluoric acid complex partially removed the *t*-

butyldimethylsilyl group to give **122** and **110**. In an attempt to remove the trimethylsilyl groups of **123** with aqueous acetic acid solution, the selective deprotection of the trimethylsilyl ether of the secondary alcohol occurred in preference to the trimethylsilylenol ether. The resulting alcohol **124** was treated with triethylamine-hydrofluoric acid complex to give a 4:1 mixture of **109** and **125**. The configuration of the isopropenyl substituent was then unambiguously determined by comparison with authentic compounds, **109** and **110** prepared from **108**.

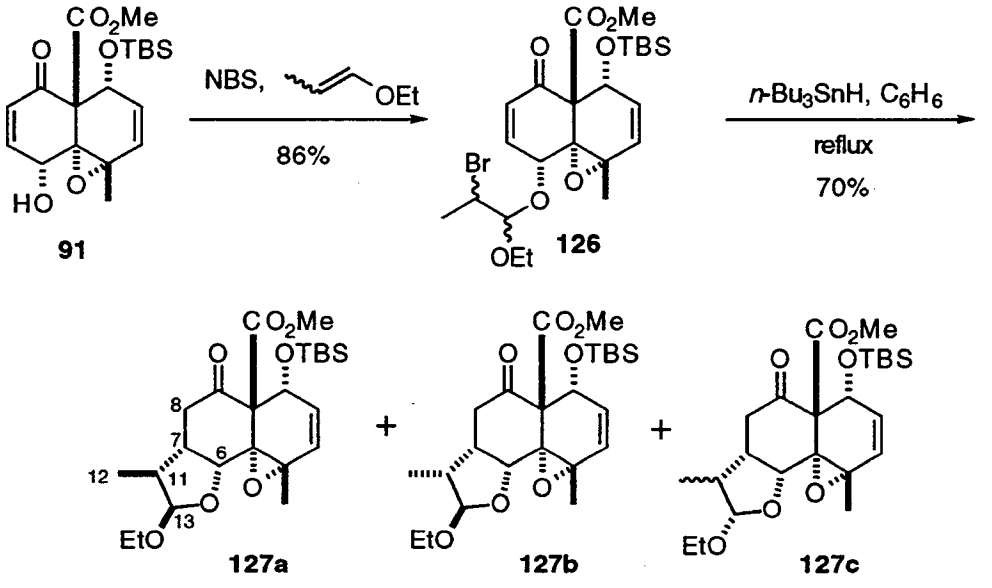


Scheme 31

The disappointing stereochemical outcome in the addition of an isopropenyl substituent to **91**, **95**, and **98** with cuprates made it necessary to

plan an alternative strategy for introducing this group. Toward this end, intramolecular radical cyclization of bromoacetal **126** was envisioned as a means of establishing the desired α configuration of the isopropenyl group.[73] The resulting *cis* fused γ-lactol could then be used for installing an α-isopropenyl group.

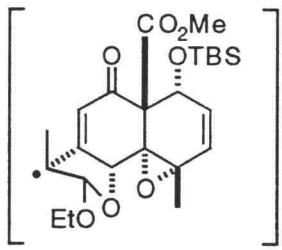
Intramolecular radical cyclization of a mixture of diastereomeric bromoacetals[74] **126** prepared from **91** was initiated with tri-*n*-butyltin hydride in the presence of 2,2'-azobisisobutyronitrile (AIBN) and afforded a mixture of **127a**, **127b**, and **127c** in the ratio of 2:5:3. (**Scheme 32**). Pure **127a** and **127b** were obtained after column chromatography, along with an inseparable mixture of the two diastereomers which corresponded to **127c**.



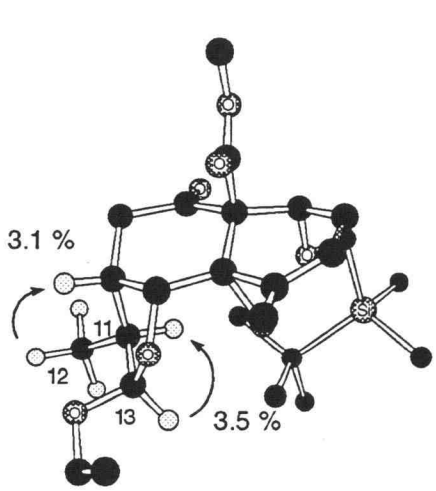
Scheme 32

The stereochemistry of **127a** and **127b** was determined by a series of nuclear Overhauser experiments (**Figure 4**). Irradiation of the C-12 methyl signal and H-13 proton of **127a** caused enhancement of the signals due to the protons H-7 and H-11 (3.1 and 3.5%,respectively). In addition, irradiation of the

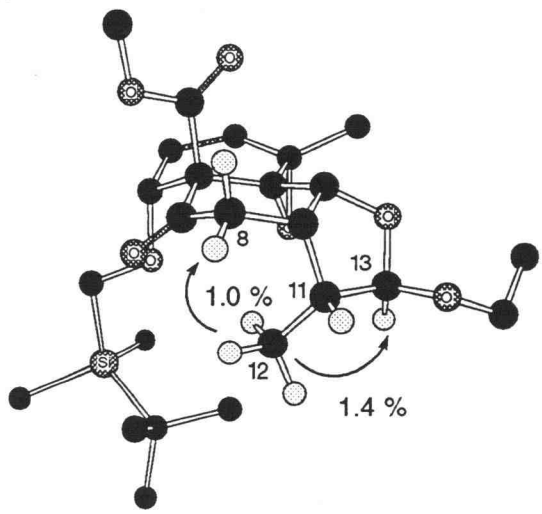
C-12 methyl signal of **127b** induced peak enhancement of the equatorial H-8 and H-13 (1.1% and 1.4%, respectively). These experiments defined the relative configuration of substituents around the perimeter of the γ-lactol segment and confirmed the *cis* fusion of the ring junction. The formation of **127b** as the major product in the cyclization of **126** is also consistent with the preferred transition state[75] proposed by Houk et al. for these radical cyclizations. According to Houk's hypothesis the preferred transition state for cyclization of the radical derived from **126** would be represented as **128**.



128



127a

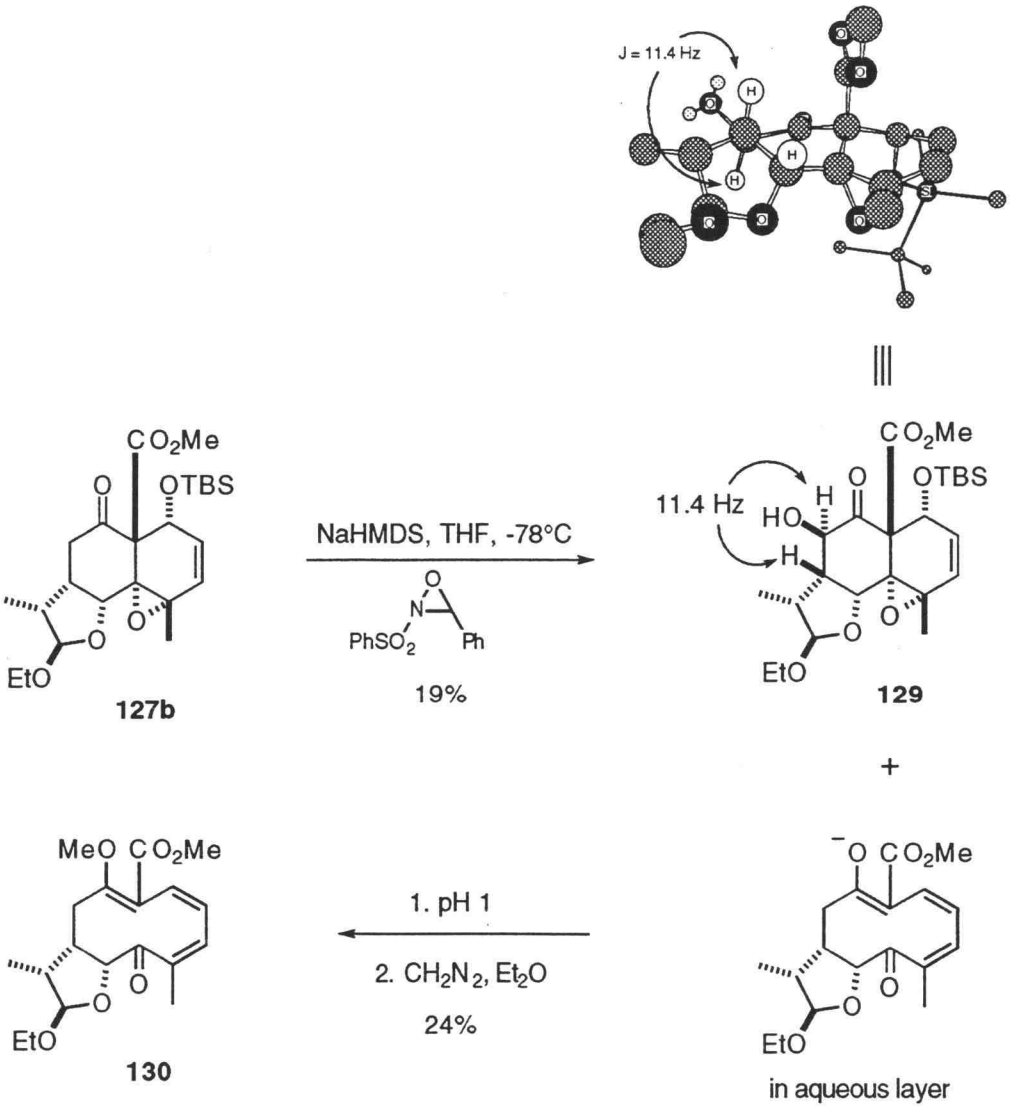


127b

Figure 4: Nuclear Overhauser Effects of **127a** and **127b**

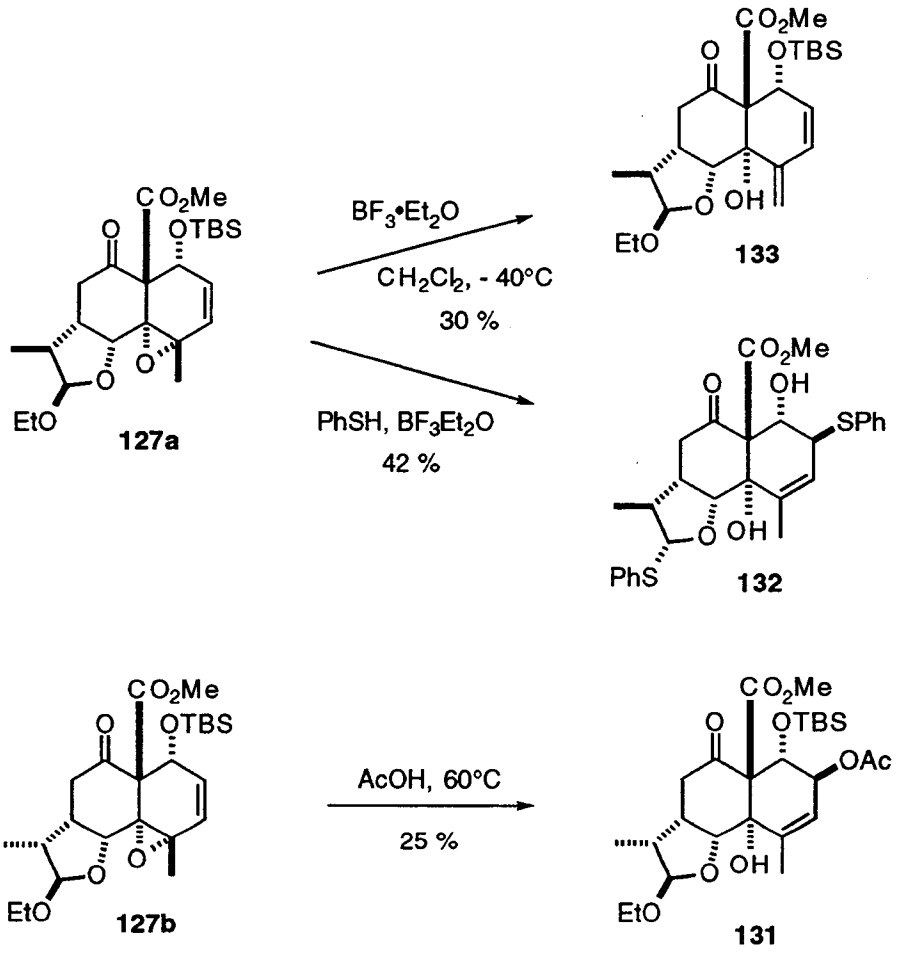
The hydroxylation of **127b** following Davis' protocol using sodium hexamethyldisilazide and Davis' oxaziridine[76] afforded only 19% of β hydroxy ketone **129** (**Scheme 33**). The same result was obtained using potassium

hexamethyldisilazide. The presumed β configuration of the introduced hydroxyl group was at odds with the coupling constant (J = 11.4 Hz) between H-7 and H-8 of **129** if the 6-membered ketone ring was present in a chair conformation. On the other hand, the coupling constant could be rationalized by a MM2 energy minimized conformation of **129** which showed the dihedral angle between H-7 and H-8 to be approximately 180°. Since TLC analysis showed very clean conversion of **127b** to **129** in spite of the low yield, the aqueous layer



Scheme 33

was acidified to pH 1 and extracted to afford an acidic product. Treatment of this product with diazomethane gave enol ether **130**. The structure of **130** was deduced by spectroscopic analysis. In particular, the ^{13}C NMR spectrum showed two carbonyl signals at 173 and 166 ppm corresponding to the vinylogous methoxy ketone and methyl ester carbonyls.



Scheme 34

Opening of the vinyl epoxide moieties of **127a** and **127b** was found to be less efficient than that of **91** and **108** (**Scheme 34**). Thus, treatment of **127b** with acetic acid at 60 °C afforded the desired allylic acetate **131** in only 25% yield along with unidentified side products. An attempt to open the lactol

fragment of **127a** with thiophenol and boron trifluoride etherate resulted in the formation of the crystalline mixed acetal **132** with concomitant deprotection of the *t*-butyldimethylsilyl group. An X-ray analysis of **132** unambiguously proved the stereochemistry which is now seen to be consistent with the nuclear Overhauser experiments (**Figure 5**). When **127a** was treated with boron trifluoride etherate, diene **133** was formed in 30% yield. The latter was not stable and decomposed to a more polar compound even at low temperature.

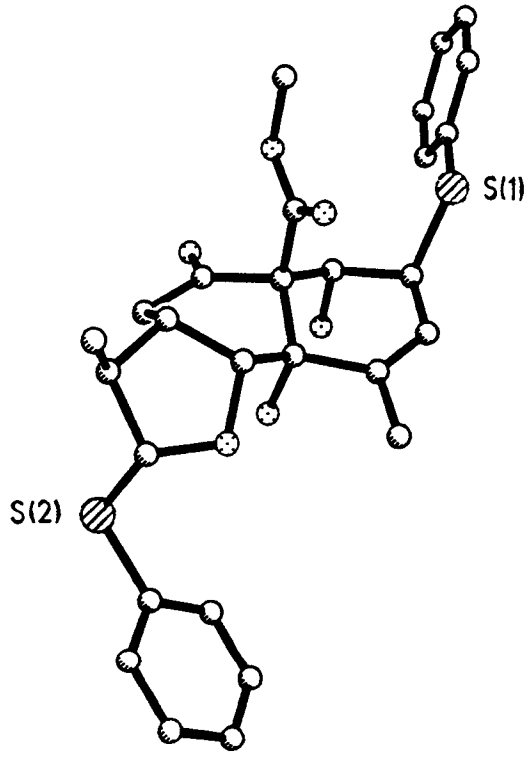
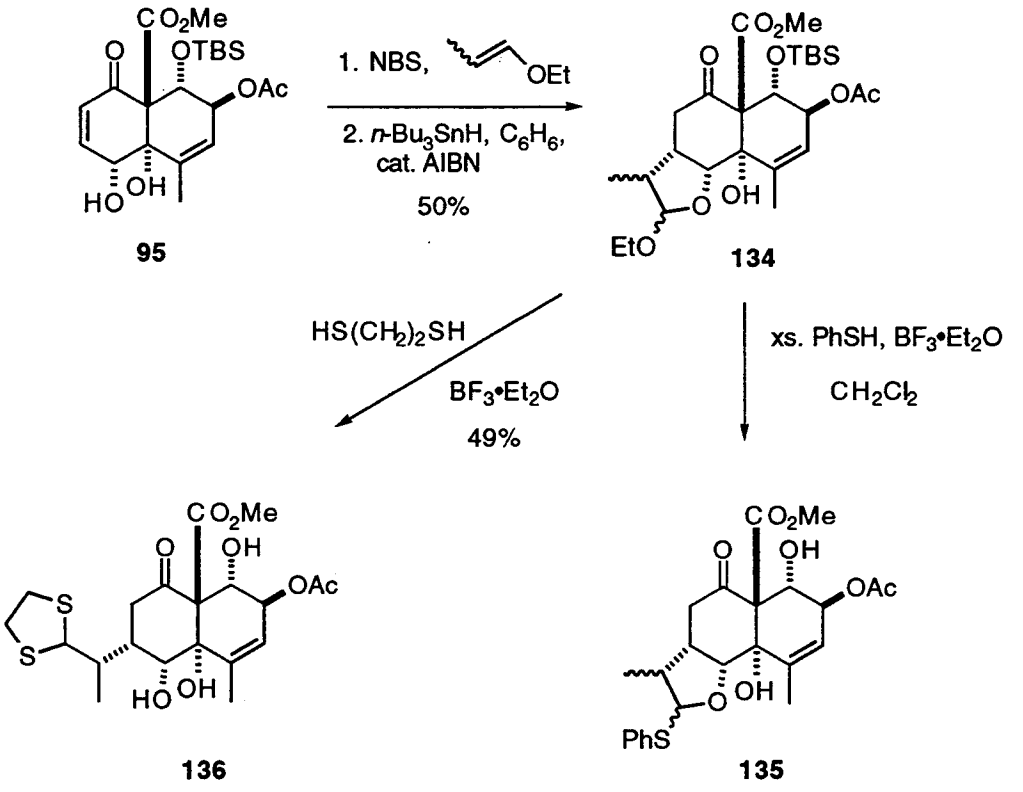


Figure 5: Pluto Diagram from X-ray Analysis of **132**

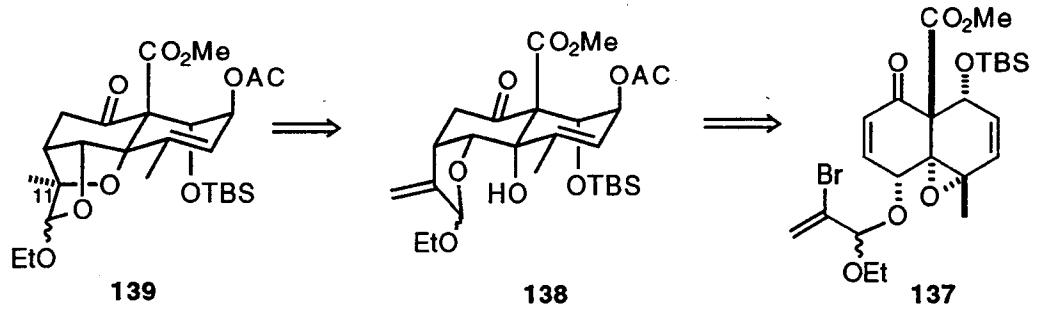
On account of these difficulties with functionalization of the vinyl epoxide moiety of **127a** and **127b**, we next attempted radical cyclization of the bromoacetal derived from **95** (**Scheme 35**). Following the protocol used with **91**, **134** was obtained as a diastereomeric mixture in 50% yield. Efforts to open

the γ-lactol of **134** with excess thiophenol and boron trifluoride etherate afforded the mixed acetal **135** with simultaneous deprotection of the *t*-butyldimethylsilyl group. When thiophenol was replaced by ethanedithiol, the dithiane **136** was obtained in 49% yield as a single isomer.



Scheme 35

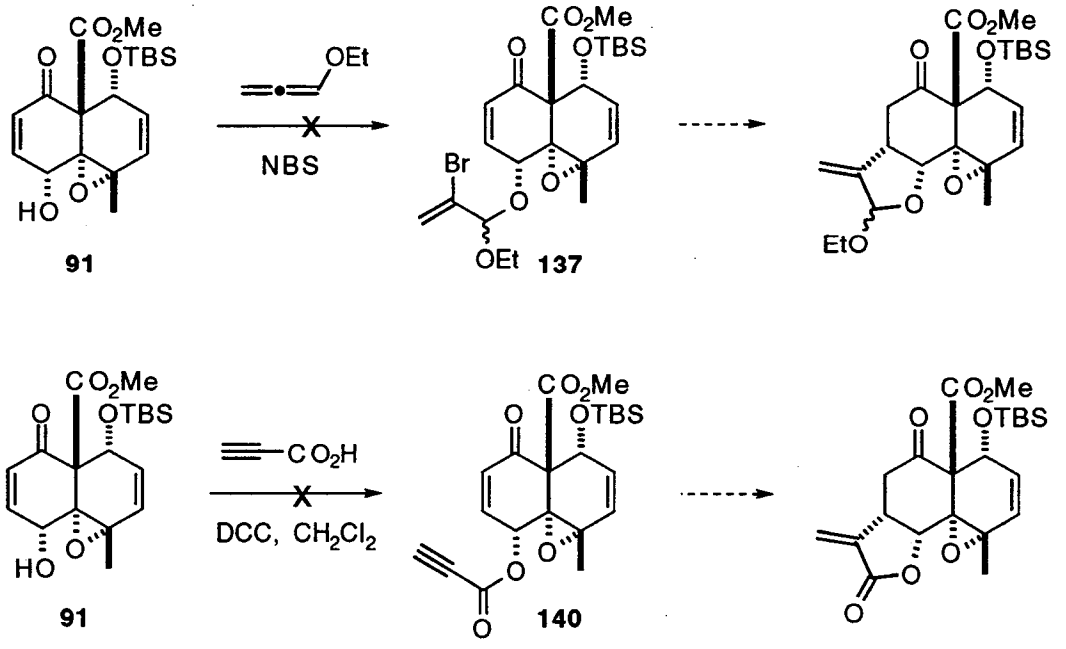
The difficulties encountered in the attempted transformation of the lactol fragment of **127a** and **127b** to an α-isopropenyl group indicated that a more highly functionalized precursor for the intramolecular cyclization was needed. This consideration led to an alternative route as depicted in **Scheme 36**. In addition to the formation of a *cis* ring fusion, this route would also control the configuration at C-11 via cyclization of the angular hydroxyl group on to the exo double bond of the lactol **138**.



139 **138** **137**

Scheme 36

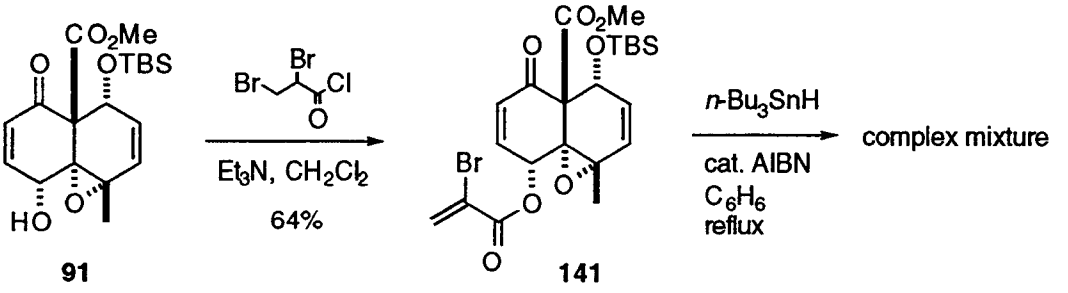
Unfortunately, attempts to prepare **137** using a modification of Moriya's procedure[77] were not successful and only a complex mixture was obtained when **91** was treated with excess of 1-ethoxyallene[78] in the presence of N-bromosuccimide. Moreover, a serious disadvantage to this reaction was the fact that the allene component must be used as a limiting reagent. Attempt to prepare propynoyl ester **140** by acylation of **91** with propiolic acid following a known procedure[79] resulted in recovery of the reactant.



91 **137** **91** **140**

Scheme 37

A more promising substrate for cyclization appeared to be the 1-bromoacrylate **141** which was obtained in good yield when **91** was treated with 1,2-dibromopropanoyl chloride in the presence of triethylamine followed by1,2-elimination of hydrogen bromide.[80] However, attempts to effect intramolecular radical cyclization of **141** resulted in the formation of a complex mixture. This is probably due to the fact that the radical cyclization is much slower than competing side reactions such as 1,4-reduction of the enone moiety or reduction of initially formed radical species. The decelerating effect of a sp^2 center on the tethered chain on the intramolecular radical cyclization is well known.[81]

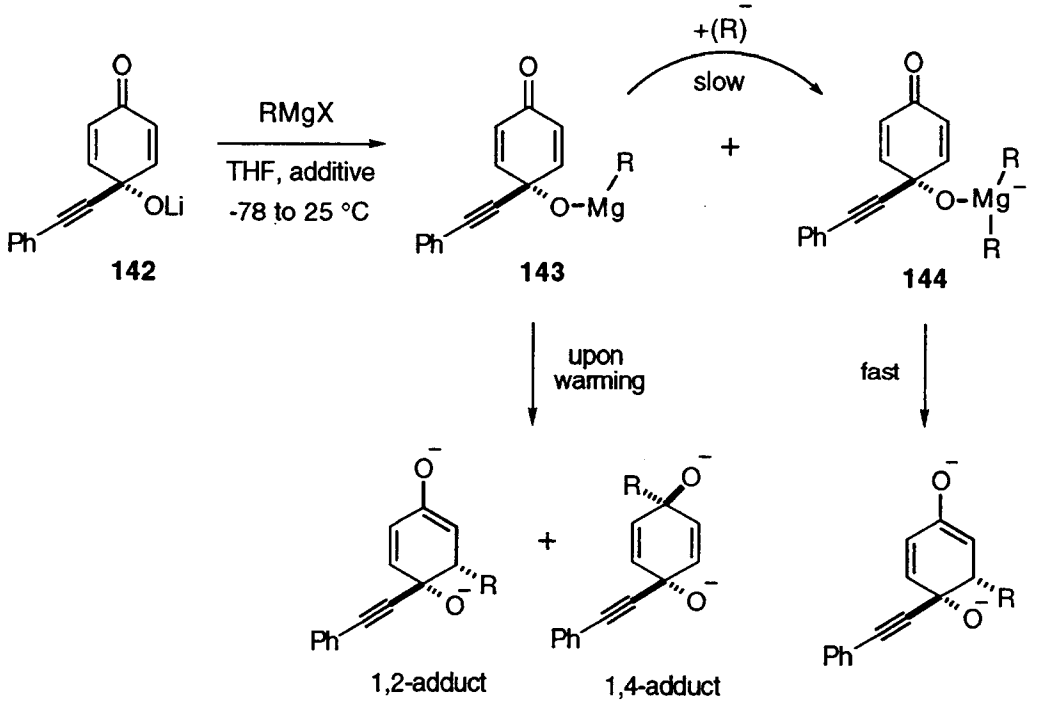


Scheme 38

Although the radical cyclization route provided a method to introduce functionality at the C-7 position with good stereochemical control, the difficulties encountered in the further manipulation of the lactol fragment as well as the vinyl epoxide moiety of the cyclized products made further progress along these lines impossible. Hence, it was necessary to reconsider our earlier strategy involving direct introduction of the isopropenyl group via conjugate addition.

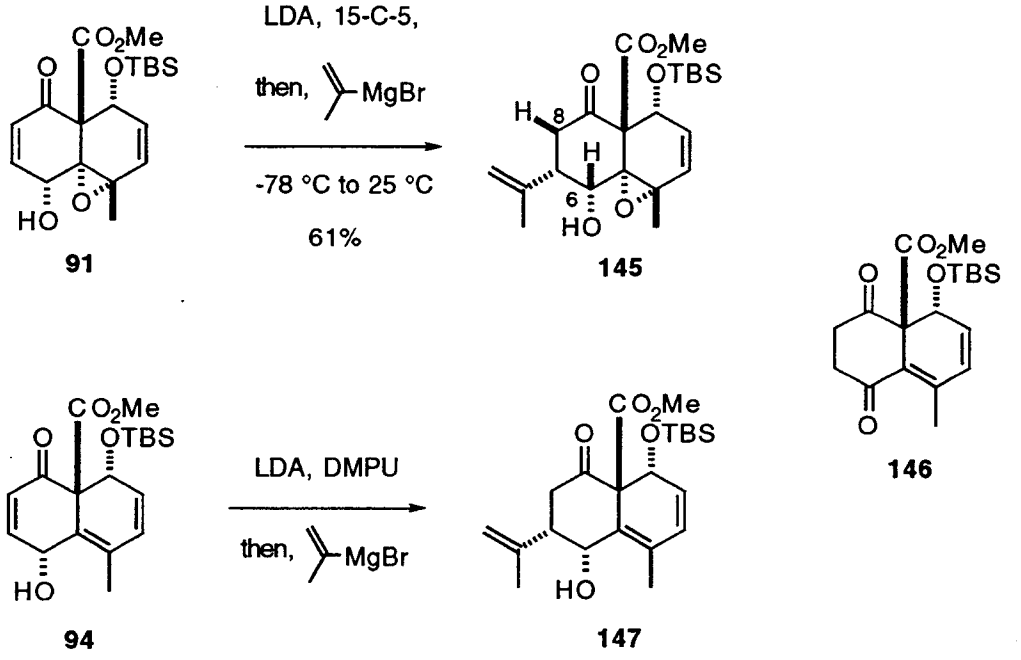
In 1989 Liotta and coworkers reported that chelation controlled conjugate addition[82] of Grignard reagents to quinoxide **142** proceeded with high *syn* selectivity with respect to the hydroxyl group (**Scheme 39**). According to the

authors, the first step of the process iinvolves formation of a naked quinoxide anion by addition of a chelating species such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) or crown ether. Subsequent addition of the Grignard reagent produces a quinoxide-Grignard binary complex **143** which equilibrates with a ternary ate complex **144** via a Schlenk equilibrium. It was suggested that the more reactive ate complex leads to chelation controlled conjugate addition at -78 °C with high 1,2-selectivity, whereas the binary complex undergoes conjugate addition above -25 °C. The ratio of 1,2 vs 1,4 addition was only slightly affected by the reaction conditions (chelating additives, counter ion of the quinoxide **142**, and Grignard reagent). However, complete diastereoselectivity was observed in both 1,2 and 1,4-additions, the Grignard reagent entering *syn* with respect to the hydroxyl group.



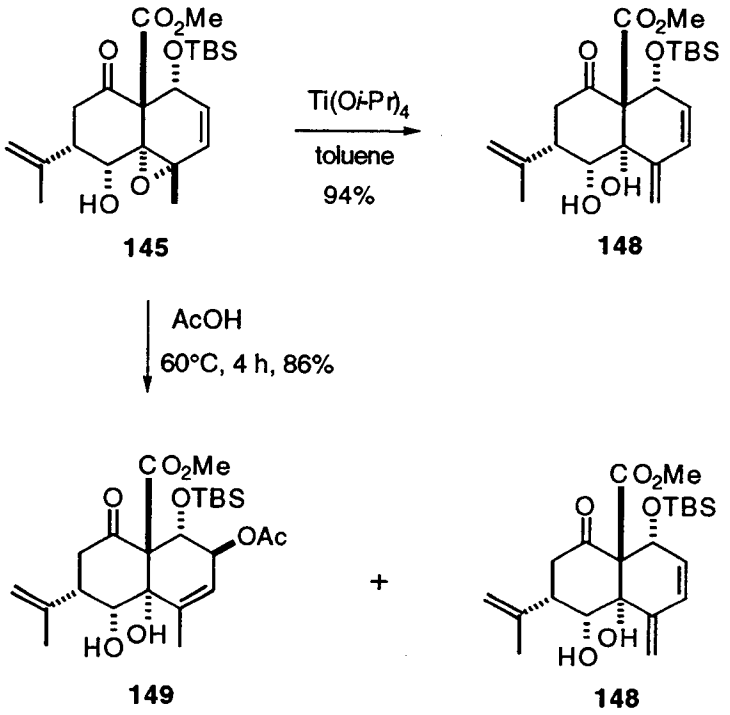
Scheme 39

After considerable experimentation, the conjugate addition of isopropenyl magnesium bromide to **91** was achieved following Liotta's procedure in 61% yield when lithium diisopropylamide (LDA) was used in the presence of 15-crown-5 (**Scheme 40**). The stereochemical outcome of the addition was easily determined by comparison of the ^{1}H NMR spectrum of **145** with that of the undesired β-isomer **108**. Interestingly, a long range W-coupling (J=1.7 Hz) between H-6 and H-8 indicated that the six-membered ring bearing the isopropenyl group had adopted a boat conformation. The α-isopropenyl group could also be introduced into enone **94** when LDA and DMPU were used. However, the yield was low (23%) and a substantial quantity of starting material was recovered. Replacement of DMPU by 15-crown-5 resulted in a complex mixture. Only dienone **146** was obtained in low yield and none of the desired product **147** was detected.



Scheme 40

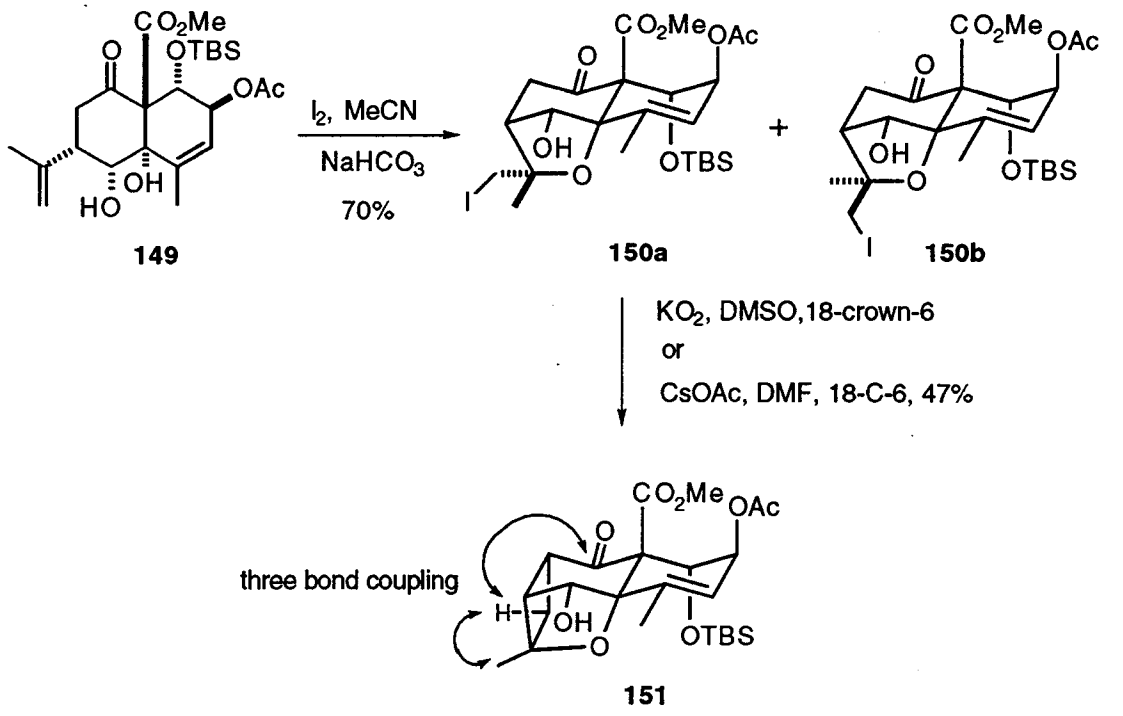
With an efficient route to **145** at hand, construction of the tetrahydrofuran ring of euonyminol (**3**) was the next objective. Towards this end, **145** was treated with titanium tetraisopropoxide for 24 h at room temperature to give diene **148** as the sole product (**Scheme 41**). On the other hand, when **145** was treated with acetic acid at 60 °C, a 7:3 mixture of allyl acetate **149** and **148** were obtained. These results are to be contrasted with the exclusive formation of **109** from the β-isopropenyl isomer **108** under the same reaction conditions and it is clear that the reversed stereochemistry of the isopropenyl group influences the course of these reactions.



Scheme 41

An initial attempt to construct the tetrahydrofuran moiety via cyclization of the angular hydroxyl group and the isopropenyl group of **149** with phenylselenyl chloride[83] was unsuccessful and gave only recovered starting material. However, iodoetherification[84] of **149** afforded a pair of iodides **150a** and **150b** in

a 4:1 ratio based on ^{1}H NMR analysis (**Scheme 42**). This mixture was inseparable by column chromatography and the stereochemical outcome of the cyclization could not be dertermined at this stage. In an attempt to transform the primary iodide of **150a** and **150b** to a hydroxyl functionality, these substances were treated with potassium superoxide in dimethyl sulfoxide in the presence of 18-crown-6.[85] Unexpectedly, the major product was cyclobutane **151**. A similar result was obtained upon the treatment of **150a** and **150b** with cesium acetate in dimethylformamide in the presence of 18-crown-6[86] and afforded **151** in 47% yield. The formation of **151** clearly arises from intramolecular alkylation[87] of the enolate of **150a**, reflecting the strongly basic character of the reagents, and thus indicates that the major product from the iodoetherification of **149** is the undesired endo iodomethyl isomer. The structure of **151** was first characterized by spectroscopic means. Thus, only one methylene carbon signal and six methine carbon signals were observed in the DEPT (Distortionless Ehancement Polarization Transfer) analysis. In the long range HETCOSY (Heteronuclear Chemical Shift Correlation Spectroscopy), one of the methylene protons showed two three-bond couplings, one of which was the methyl group on the tetrahydrofuran moiety and the other with the ketone carbon. This strongly hinted at the presence of a cyclobutane. Subsequently, an X-ray crystal structure of **151** confirmed the presence of the cyclobutane (**Figure 6**) and therefore the structure of the major stereoisomer from **149** to be **150a**.



Scheme 42

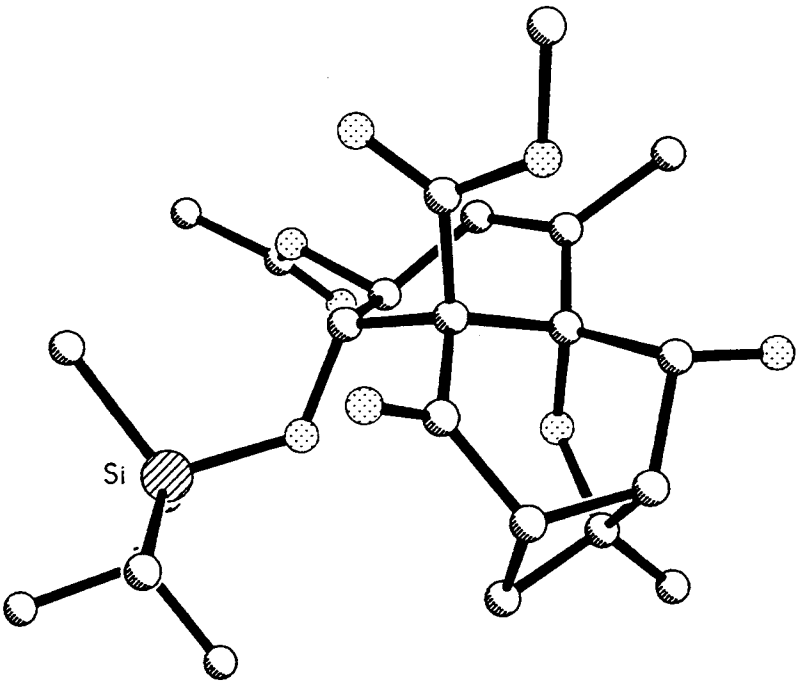
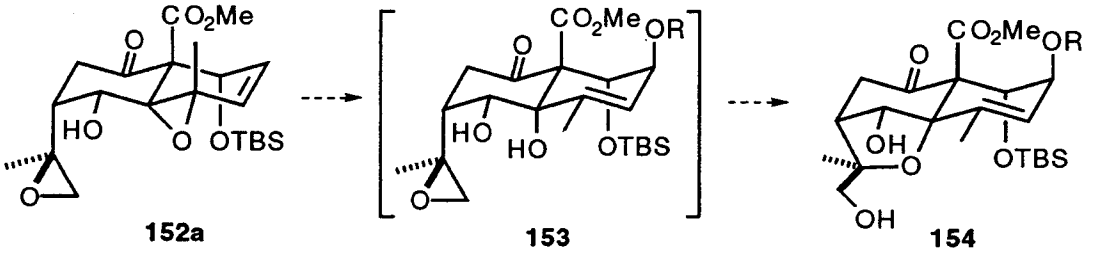


Figure 6: Pluto Diagram from X-ray Analysis of **151**

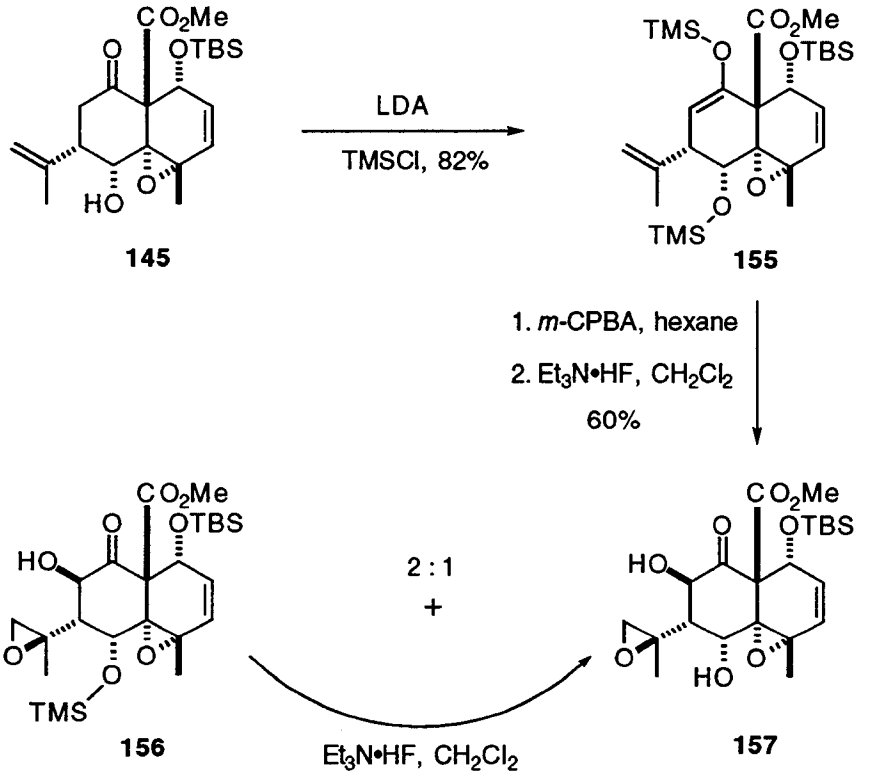
This disappointing stereochemical result coupled with the difficulties associatiated with manipulation of the iodide functionality of **150** indicated that a different strategy would be necessary to construct the tetrahydrofuran segment of euonyminol (**3**). In this regard, a sequence involving consecutive opening of epoxides in a structure such as **152a** was considered to be an alternative strategy as depicted in **Scheme 43**. It was hoped that this epoxide "cascade" could be triggered by an *anti* S_N2' opening of the vinyl epoxide moiety with a suitable alkoxy nucleophile to give **153**, which would then initiate opening of the second epoxide[88] to form **154**. Formation of the tetrahydrofuran ring of **154** by this process brings forth two crucial stereochemical issues, the configuration of the disubstituted epoxide in **152a** and the assumption that the epoxide in **153** undergoes attack by the angular hydroxy group in a 5-*exo*-tet fashion with inversion at the quarternary carbon.



Scheme 43

With the isopropenyl substituent of **145** now correctly installed, this ketone became a focal point for introduction of the remaining oxygen substituents. To this end, treatment of **145** with LDA and TMSCl afforded enol ether **155** in 82% yield. Simultaneous epoxidation of the enol ether and the isopropenyl double bond of **155** with *m*-chloroperbenzoic acid, followed by exposure to the triethylamine-hydrofluoric acid complex, gave a mixture of **156** and **157** in a ratio of 2:1 (**Scheme 44**). The epoxidation was, as expected,

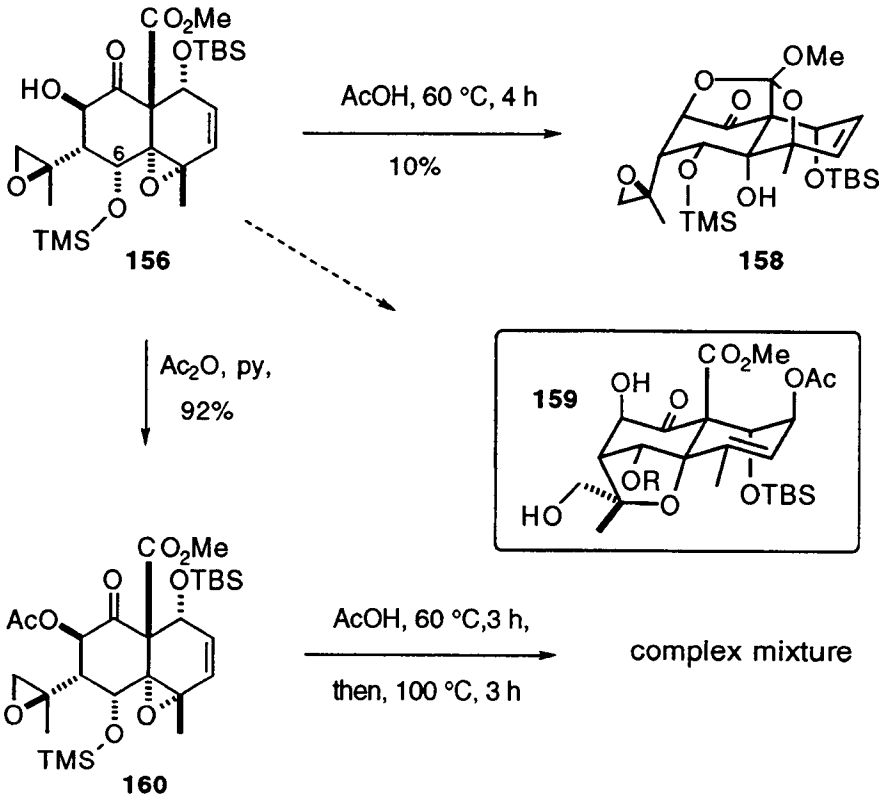
highly stereoselective at the enol ether placing the hydroxyl substituent in the β configuration exclusively. To our surprise, the terminal epoxide moiety was also formed with high stereoselectivity since **156** and **157** had the same epoxide configuration as evidenced by the conversion of **156** to **157** with triethylamine-hydrofluoric acid complex. However, the configuration could not be determined at this stage. Subsequently, it was found later that the undesired isomer was predominant by comparison of the minor product to authentic **157** prepared independently by hydroxylation of **152b**.



Scheme 44

When the major product **156** was treated with acetic acid at 60 °C in the hope of initiating the epoxide "cascade", only a low yield of the orthoester **158** was obtained (**Scheme 45**). It was thought that the failure to obtain the desired tetrahydrofuran **159** could be due to the blocked hydroxyl group at C-6 and

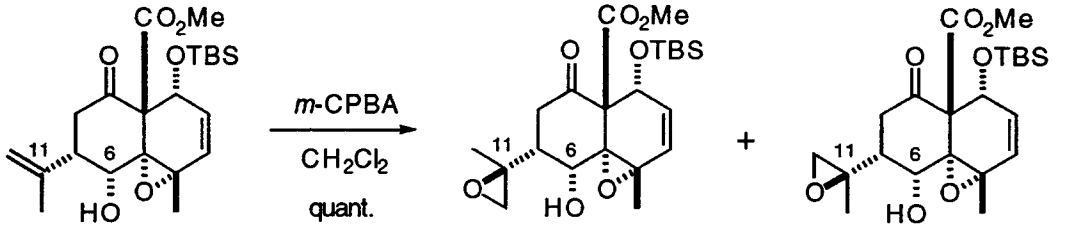
therefore **157** was subjected to the same conditions. However a complex mixture resulted. A careful conformational analysis of these results suggested that the α-hydroxy ketone moiety of **156** may prevent the saturated six-membered ring from adopting the chair conformation required for the cascade cyclization to take place. Accordingly, the hydroxyl group of **156** was protected as acetate **160**, but attempted cyclization of this material was unproductive below 60 °C and yielded a complex mixture when the reaction temperature was raised to 100 °C.



Scheme 45

Since the α-hydroxy ketone moiety of **156**, **157**, and **160** appeared to interfere with the epoxide cascade reaction, we turned our attention to the diepoxide **152a** and **152b** (**Scheme 46**). These diepoxides were initially

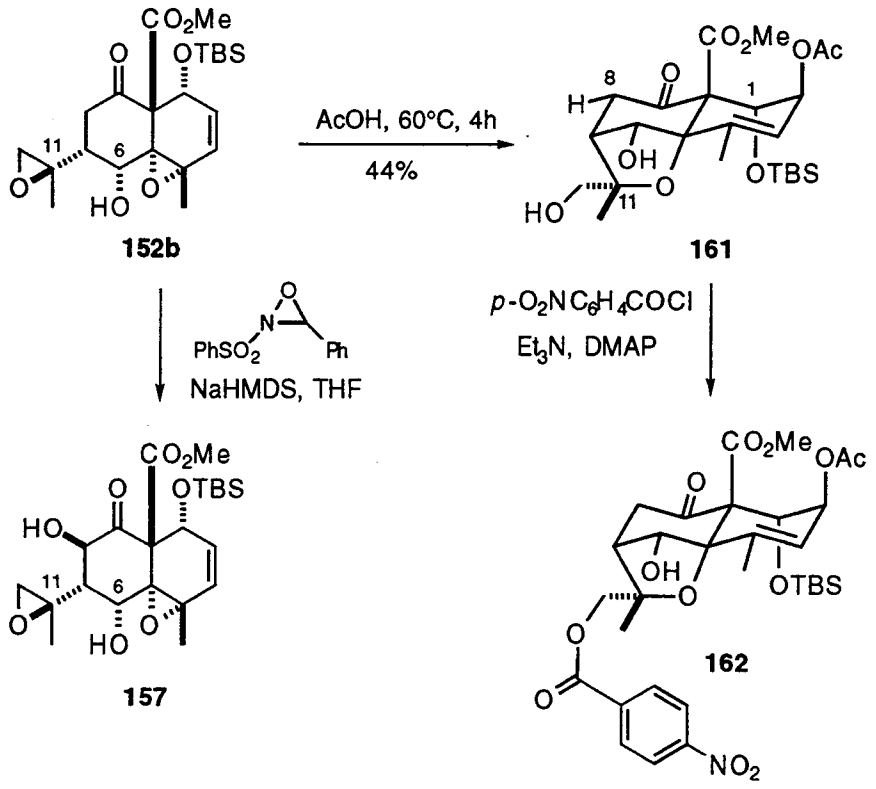
prepared in quantitative yield as a 1:1 mixture by treatment of **145** with *m*-chloroperbenzoic acid. The pure stereoisomers **152a** and **152b** were isolated after column chromatography, however with the stereochemistry at C-11 still undetermined.



145 **152a** **152b**

Scheme 46

When pure **152b** was treated with acetic acid at 60 °C, diol **161** was isolated in 44% yield (**Scheme 47**). The configuration of the newly formed quaternary center at C-11 of **161** was initially deduced by from a nuclear Overhauser experiment in which peak enhancement of the equatorial proton at C-8 was observed by irradiation of the methylene protons adjacent to the primary hydroxyl group. Subsequently, the structure of **161** was unambiguously confirmed by X-ray analysis of *p*-nitrobenzoate derivative **162** (**Figure 7**). Assuming that the stereochemical integrity of the epoxide was preserved in the tetrahydrofuran formation step, the configuration of the parent epoxide could be deduced as **152b**. In a separate experiment, Davis' hydroxylation of **152b** and comparison of the ^{1}H NMR of the product with that of minor product **157** obtained from the enol ether **155** established the configuration of the epoxide moiety of **156** and **157** as shown (**Scheme 44**).



Scheme 47

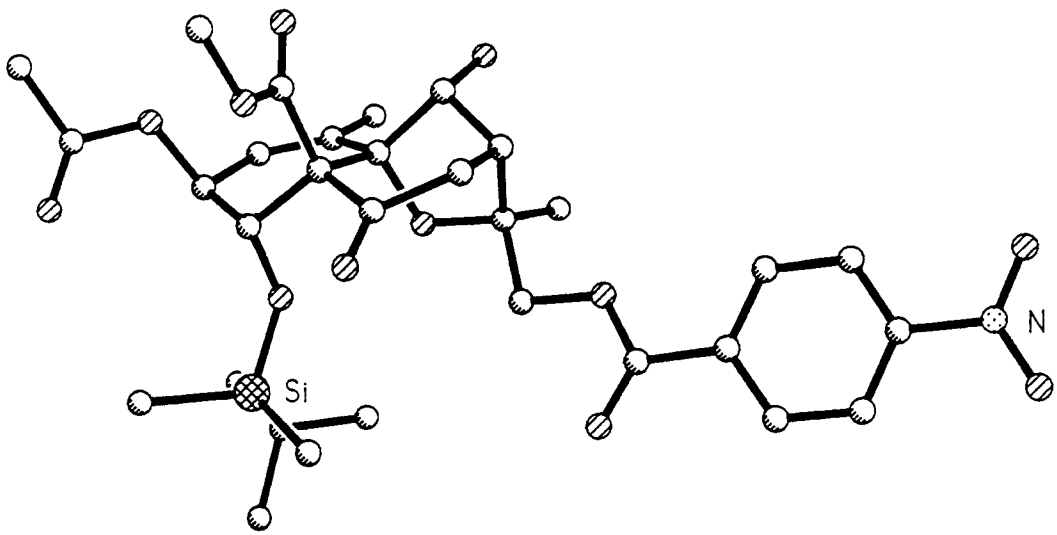
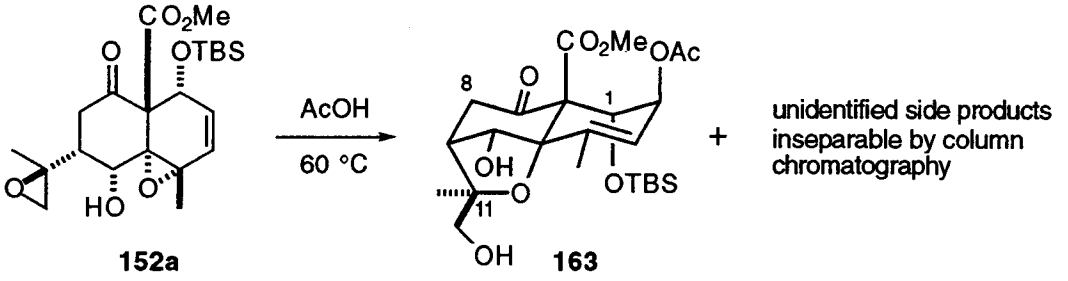


Figure 7: Pluto Diagram from X-ray Analysis of **162**

Having identified the configuration of the terminal epoxide of **152b** as the result of our intended cyclization, albeit with the wrong stereochemistry, attention was next turned to **152a** as a substrate for this epoxide cascade. Under the same reaction conditions as for **152b**, **152a** gave a mixture of products, which contained 30% of **163** along with unidentified side products inseparable by column chromatography (**Scheme 48**).

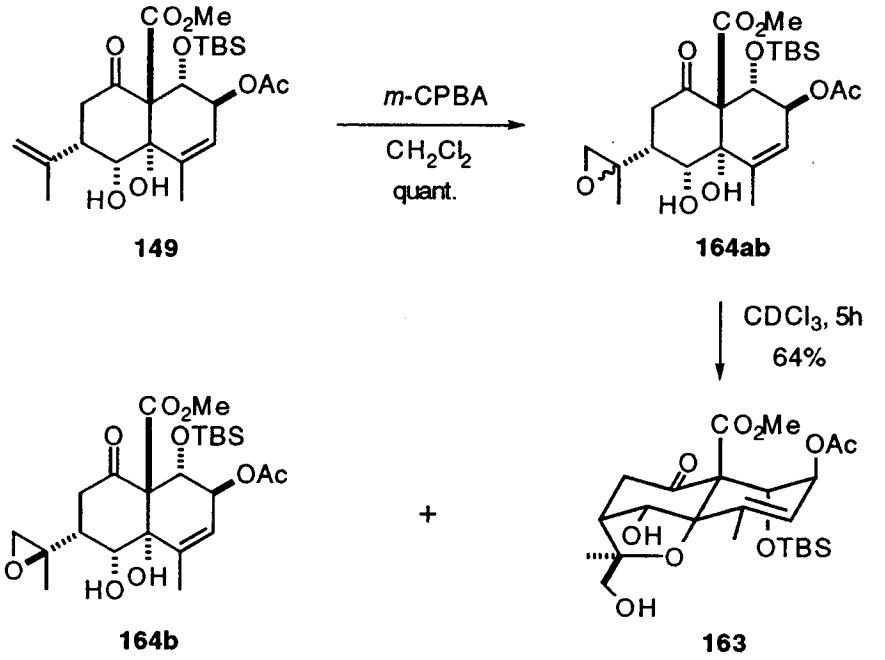


152a **163**

Scheme 48

The efficient conversion of **145** to **149** demonstrated that the first epoxide opening step of the cascade reaction proceeded smoothly, implying that formation of the tetrahydrofuran ring was the cause of the low yield. With the goal of improving this latter transformation, acetate **149** was epoxidized using 1.1 equivalents of *m*-chloroperbenzoic acid to afford a 1:1 stereoisomeric mixture of epoxides **164a** and **164b** (**Scheme 49**). Selective epoxidation of the isopropenyl double bond in preference to the trisubstituted double bond to this reagent is noteworthy since more substituted olefins are generally more reactive. In particular, trisubstituted double bonds are usually much more easily epoxidized than 1,1-disubstituted alkenes. The low reactivity of the trisubstituted double bond in this case may be the result of reduced electron density caused by the two adjacent hydroxyl groups through $\pi \rightarrow \sigma^*$ interaction or it could be due to a steric effect. When a mixture of isomers of **164a** and

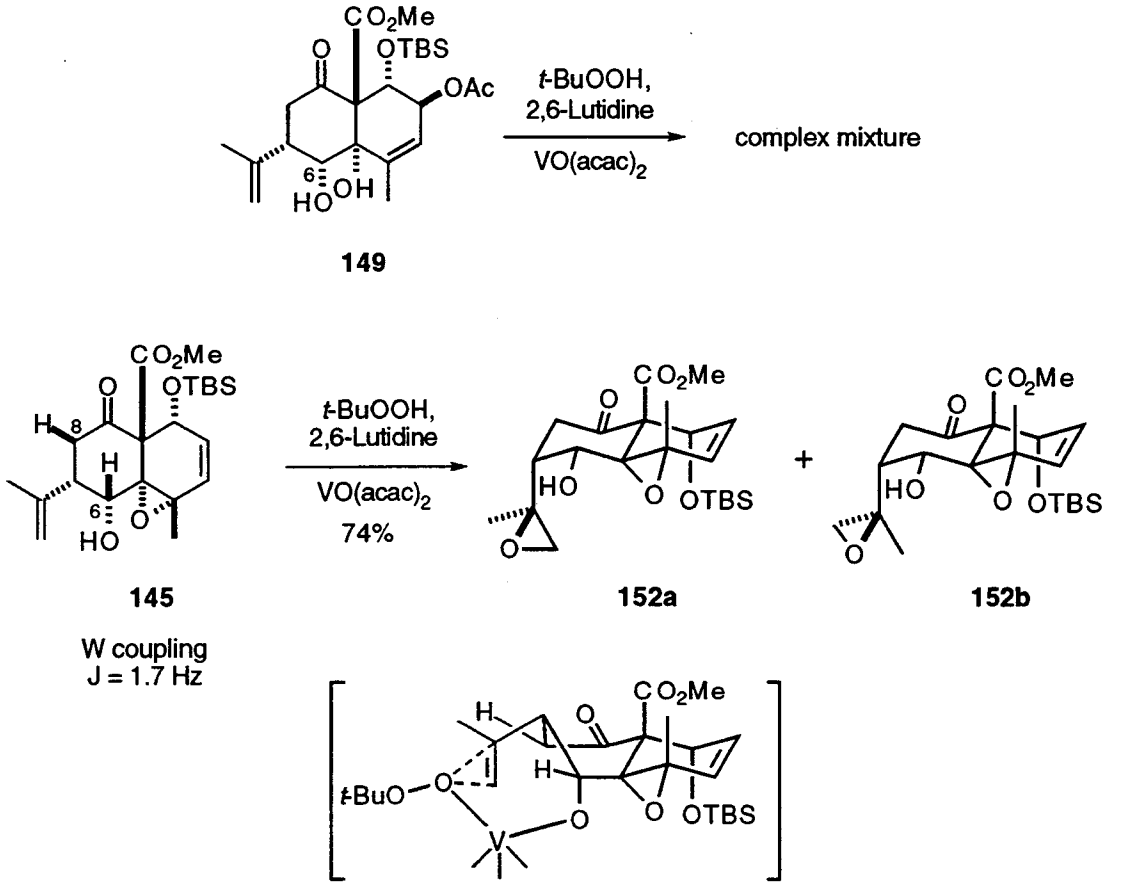
164b was kept in deuterated chloroform at room temperature for 5 h, one of the two isomers **164a** was completely consumed to afford **163** in pure form after chromatography, while the isomer **164b** was recovered largely unchanged under these conditions.



Scheme 49

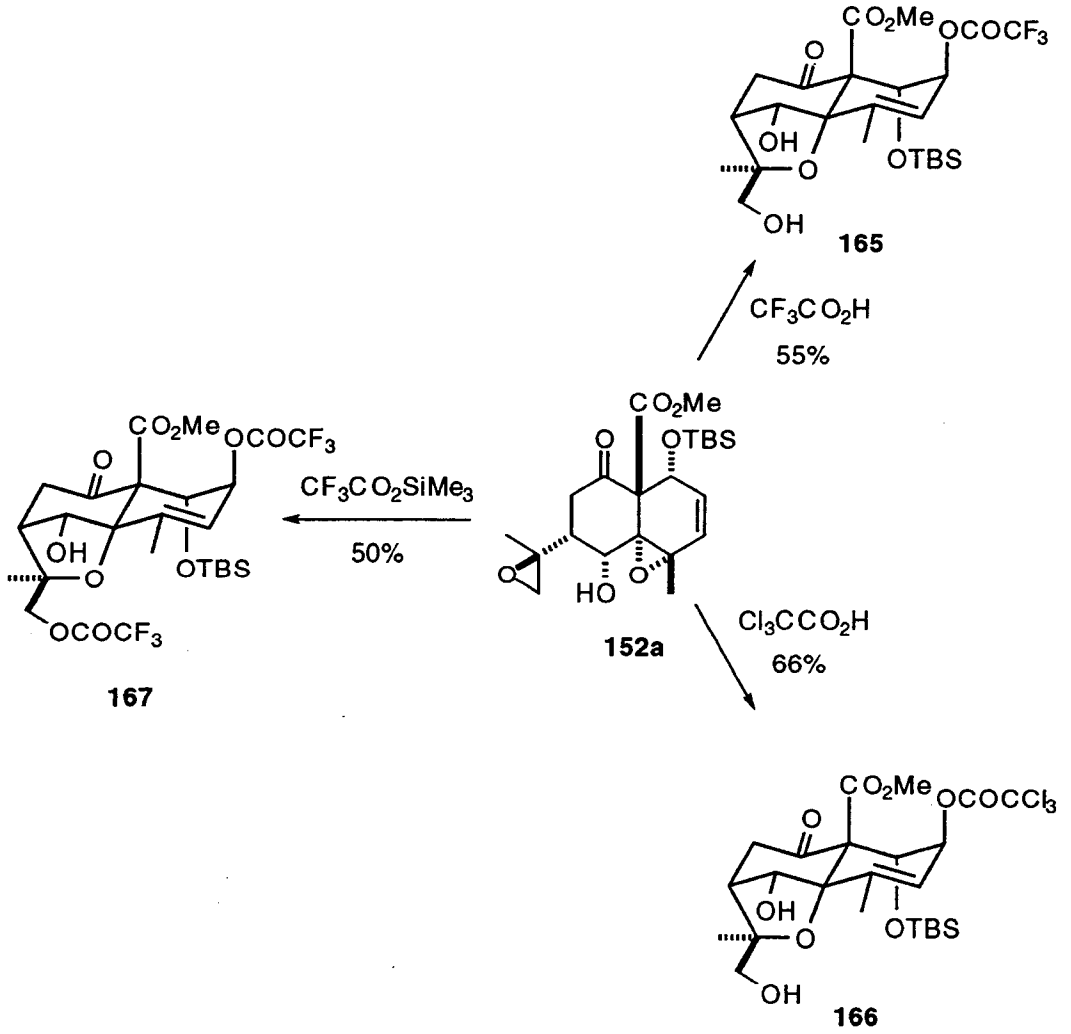
The foregoing results indicate that if **164a** could be prepared selectively, then the epoxide cascade sequence leading to **163** could become highly efficient. However, it turned out that the C-6 homoallylic hydroxyl group directed epoxidation of the isopropenyl double bond under vanadium catalysis[89] resulted in the formation of a complex mixture. Due to the failure of the stereoselective epoxidation of **149**, it was necessary to reexamine the epoxide cascade reaction of diepoxide **152a**. Crucial to the success of this strategy is the selective formation of **152a** and optimization of the epoxide cascade reaction of this diepoxide. After a series of optimizations, the stereoselectivity of the epoxidation of **145** was increased to 3:1 in favor of the desired epoxide

152a when vanadium oxyacetylacetonate in the presence of *t*-butyl hydrogen peroxide and 2,6-lutidine[90] was used. A plausible representation of the transition state in the boat conformation leading to the major isomer **152a** is shown in **Scheme 50**. This transition state presumes a boat conformation of the cyclohexanone ring of **145** since the W-coupling between H-6 and H-8 supports a boat conformation and this is the only conformer which permits directed epoxidation to the α(si) face of the isopropenyl substituent. It is also worthy of note that the presence of 2,6-lutidine was found to be essential for a good yield in this epoxidation.



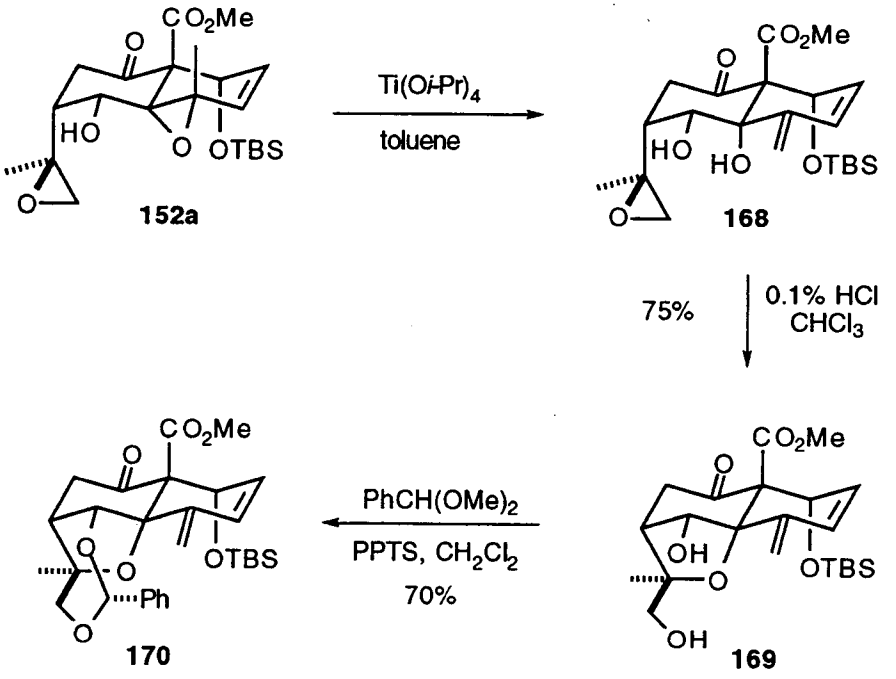
Scheme 50

The modified conditions that were developed for the earlier conversion of **91** to **96** were now applied to **152a** and were found to be remarkably efficient (**Scheme 51**). Thus, treatment of diepoxide **152a** with 1.5 equivalent of trifluoroacetic acid in chloroform gave trifluoroacetate **165** in 55% yield. When trifluoroacetic acid was replaced by trichloroacetic acid, trichloroacetate **166** was obtained in 66% yield. Unexpectedly, di-trifluoroacetate **167** was isolated when trimethylsilyl trifluoroacetate[91] was employed. An obvious advantage in the use of these trifluoro and trichloro esters is the facile cleavage which can be expected under basic conditions for **165** and **166**.



Scheme 51

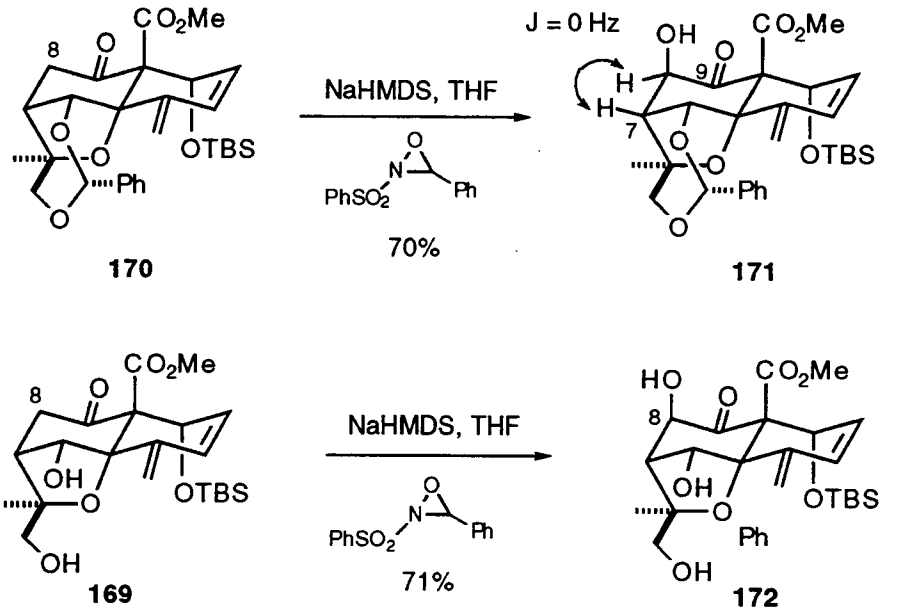
In parallel with these investigations, another route to euonyminol starting from the diene **168** was explored. This diene was obtained from **152a** by treatment with titanium tetraisopropoxide in toluene (**Scheme 52**). Cyclization of **168** was accomplished in acidic chloroform solution to give diol **169** in good yield. The crude product was treated with benzaldehyde dimethyl acetal in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate to afford the benzylidene acetal **170** as a single isomer. By contrast, an attempt to form an acetonide of **169** was completely unsuccessful.



Scheme 52

The efficient preparation of **170** made available a substrate upon which further structural modifications in the direction of euonyminol could be examined. One of these was introduction of the axial hydroxyl substituent at C-8, for which the adjacent ketone was conveniently at hand. To our pleasant surprise, hydroxylation of the enolate of **170**, generated with sodium

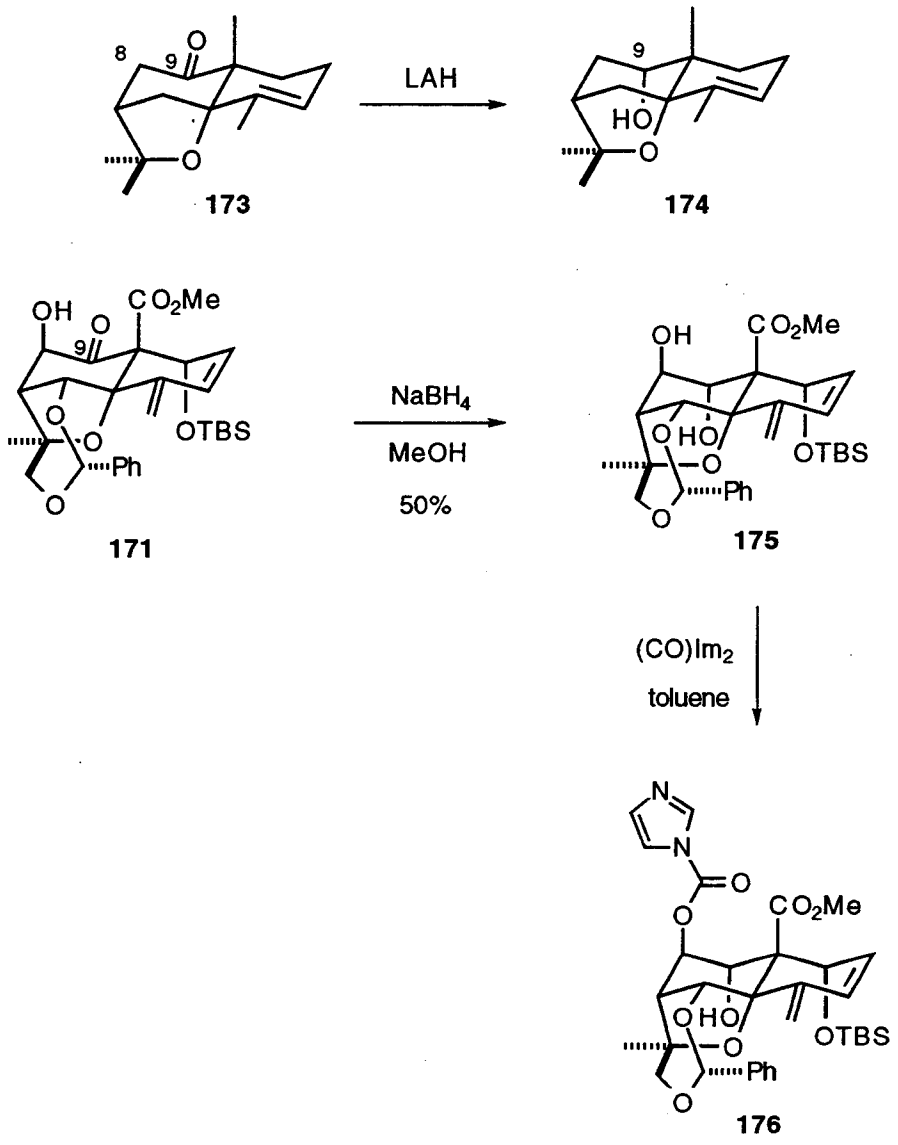
hexamethyldisilazide, with Davis' oxaziridine afforded **171** with high diastereoselectivity (**Scheme 53**). Under similar conditions using 3.2 equivalent of sodium hexamethyldisilazide, the unprotected diol **169** could also be hydroxylated to form triol **172** in 71% yield. The coupling constant (J=0 Hz) between H-7 and H-8 indicated initially the β configuration of the introduced hydroxyl group at C-8. Subsequently, an X-ray analysis of a later intermediate confirmed this assignment.



Scheme 53

Reduction of the C-9 ketone of **171** to form the desired 9β-ol **177** appeared to be problematic at the outset due to the steric congestion surrounding the bottom face of the molecule. A report[92] by Huffman provides an illustrative example of this steric impedence in the reduction of **173**. With lithium aluminum hydride this dihydroagarofuran system afforded 9α-alcohol **174** exclusively, whereas a dissolving metal reduction gave the 9β-alcohol. Unfortunately, a dissolving metal reduction would be incompatible with the

functionalities present in **171**, including diene, benzyl and α-hydroxy ketone moieties. Although selective formation of the 9β-alcohol **178** from **171** with metal hydride reducing reagents appeared unpromising for steric reasons, there



173 **174** **171** **175** **176**

Scheme 54

remained possibility that attack by hydride from the α face of the hydroxy ketone moiety of **171** could be induced if the six-membered ring exist in a distorted chair conformation. In the event, reduction of **171** by sodium

borohydride in methanol afforded a diol (**Scheme 54**). Although the stereochemical outcome of the reduction could not be established from the coupling constant (J=5.1 Hz) between H-8 and H-9, our assignment was based on precedent favored *trans* diol **175**. In agreement with this assignment, treatment of **175** with carbonyl diimidazole afforded imidazolide **176** rather than a cyclic carbonate. Finally, X-ray analysis of **176** provided unambiguous proof of the *trans* configuration of **175** and also showed that the six-membered ring bearing the two hydroxyl groups occupied a boat conformation (**Figure 8**).

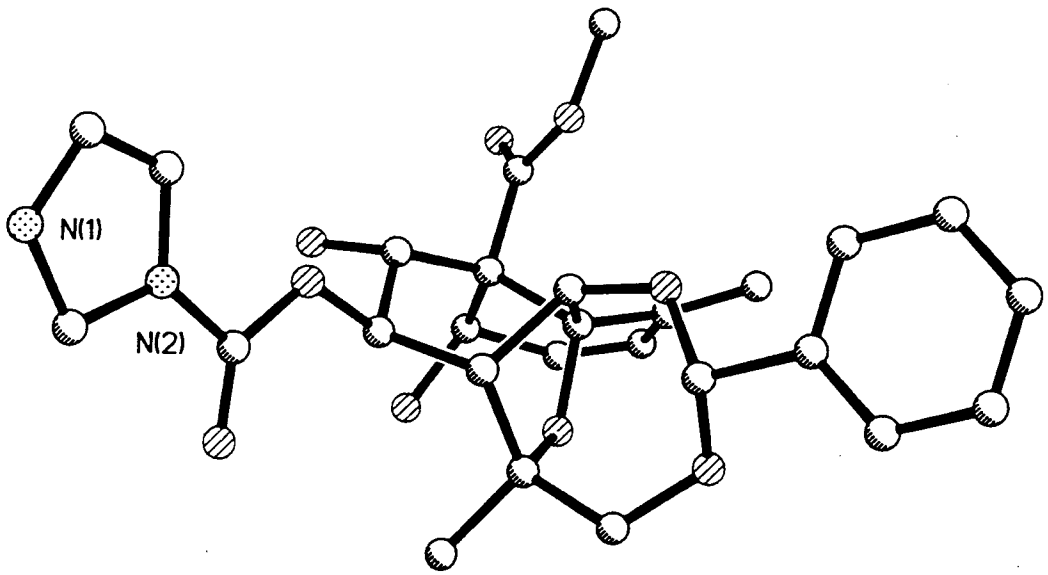
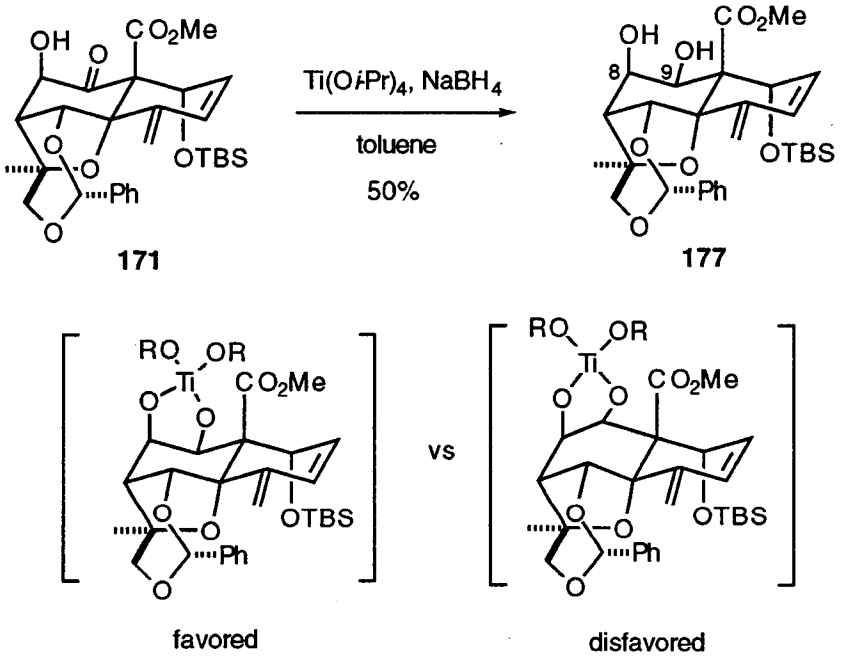


Figure 8: Pluto Diagram from X-ray Analysis of **176**

The exclusive formation of the undesired stereoisomer **175** from the reduction of **171** with sodium borohydride prompted a search for alternative reducing systems which might reverse this stereoselectivity. It was speculated that reduction of **171** in the presence of a system which allowed for chelation between the α-hydroxyl group and the ketone would lead to hydride delivery

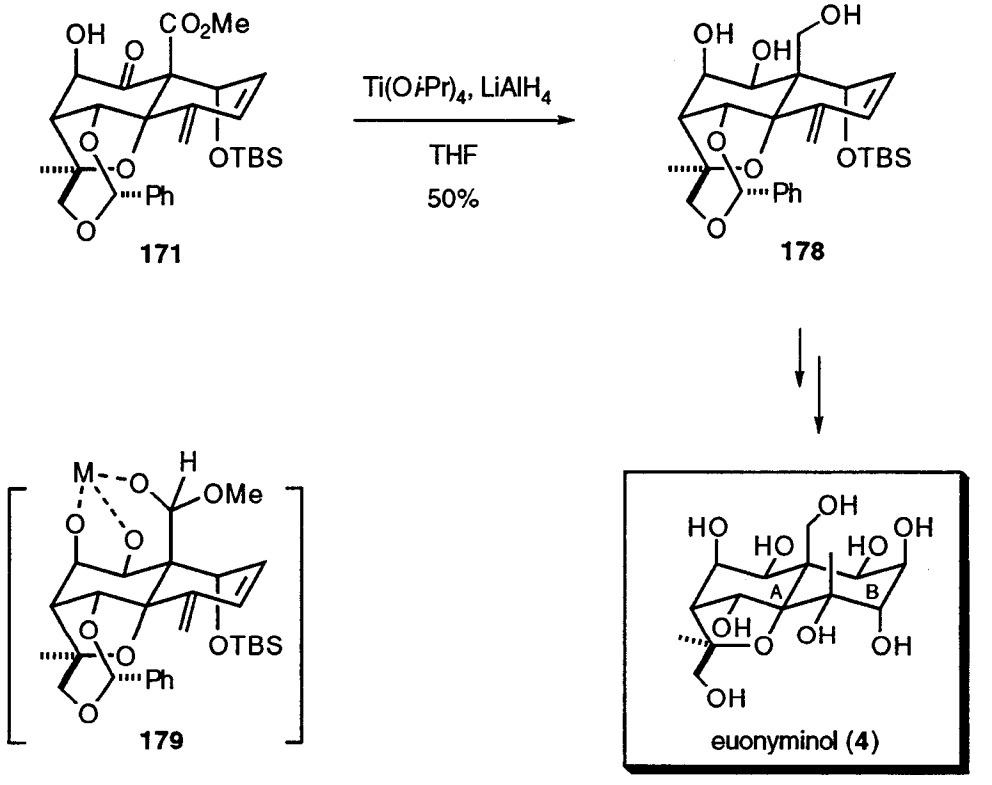
from the bottom face if the chelation of the resultant *cis* diol was energetically more favorable than that of *trans* diol in the transition state (**Scheme 55**). Following this rationale, **171** was exposed to a combination of titanium tetraisopropoxide and sodium borohydride.[93] The choice of titanium tetraisopropoxide as chelating agent was based on the known complexation of this reagent with the α-hydroxyl carbonyl moiety of tartarate in the Sharpless asymmetric epoxidation[94] of allylic alcohols. This reducing system operated smoothly on **171** to afford the desired *cis* diol **177** in 50% yield. The ^{1}H NMR spectrum of **177** showed a coupling constant (J=10.4 Hz) between H-8 and H-9 significantly larger than that (J=5.1 Hz) of the *trans* diol **175**.



Scheme 55

An attempt to reduce both the ketone and ester groups of **171** with lithium aluminum hydride and titanium tetraisopropoxide afforded triol **178** in 30% yield (**Scheme 56**). The low yield was thought to be the result of slow decomposition of the tetrahedral intermediate **179** formed by the hydride

addition to the ester group. In the TLC analysis of reaction's progress, an unidentified major spot was detected in addition to the *cis* diol **177** and the triol **178**. It was speculated that the unidentified product was the aldehyde formed by decomposition of **179** on silica gel. Accordingly, an excess of methanol and sodium borohydride (10 equiv.) was added at the end of reaction to induce breakdown of tetrahedral intermediate **179** and reduce the subsequently formed aldehyde.[95] Using this modified workup procedure, the yield of triol **178** was increased to 50%.



Scheme 56

This sequence completes the functionalization of the A ring of euonyminol and leaves only relatively minor transformations in the B ring for the final assault on **4**. Among these is the need to invert the hydroxyl groups at C-1 and the introduction of hydroxyl groups from the α face at C-3 and C-4. These

last steps remain for others to execute, and while they may appear relatively trivial it is likely that surprises lurk in the densely functionalized framework of this molecule.

In summary, the synthesis of the A ring of euonyminol (**4**) has been completed. Several substances already prepared, including **178** and intermediates such as **165** and **166** can be envisioned as a direct precursors to euonyminol. In addition, some noteworthy transformations were found along the synthetic routes investigated. These include the chemo- and stereoselective reduction of **93** to **94**, the complementary stereocontrol in the conjugate addition to **91**, a remarkably efficient construction of the dihydroagarofuran framework of euonyminol via the epoxide cascade reaction, and a stereoselective reduction of ketol **171** to **177** or to triol **178** using a hydride reagent in the presence of titanium tetraisopropoxide. The synthesis of euonyminol, while not yet complete, has been advanced to a stage where a plausible finale can be foreseen. When a synthetic route to this core unit of Cathedulin K-19 (**3**) has been established, the second phase of the project, which will involve selective acylation of the nine hydroxyl group of **4** with cathic and edulinic acids, can begin.

Experimental Section

General

Starting materials and reagents were obtained from commercial sources and, unless stated otherwise, were used without further purification. Solvents were dried by distillation from the appropriate drying agent immediately prior to use. Toluene, tetrahydrofuran, and ether were distilled from potassium and benzophenone under an argon atmosphere. Diisopropylamine, triethylamine, diisopropylethylamine, dimethylformamide, acetonitrile, pyridine and dichloromethane were distilled from calcium hydride under argon. All solvents used for routine isolation of products and chromatography were reagent grade and glass distilled. Moisture and air sensitive reactions were carried out under an atmosphere of argon. Alkyllithium reagents, sodium hexamethyldisilazide, and potasium hexamethyldisilazide were titrated following Kofron's procedure.[96]

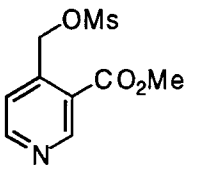
Concentration *in vacuo* refers to the use of a rotary evaporator at water aspirator pressure. Residual solvent was removed by vacuum pump at pressures less than 2 torr. Reaction flasks were flame dried under a stream of argon. Syringes were oven dried at 200 °C and cooled to room temperature in a desiccator over anhydrous calcium sulfate.

Analytical thin layer chromatography (TLC) was conducted using E. Merck precoated glass TLC plates (0.25 mm layer thickness of silica gel 60 F-254). Spots were visualized by ultraviolet light, or by heating the plate after dipping in a 3-5% solution of phosphomolybdic acid in ethanol, 10% ammonium molybdate, or a 1% solution of vanillin in 0.1M H_2SO_4 in methanol. Flash chromatography was carried out using E. Merck silica gel 60 (230-400 mesh ASTM). Radial chromatography was carried out on individually prepared rotors

with layer thickness of 1, 2 or 4 mm using a Chromatotron manufactured by Harrison Research, Palo Alto, California.

Melting points were measured using a Büchi melting point apparatus. Infared (IR) spectra were recorded with a Nicolet 5DXB FT-IR spectrometer. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained using either a Bruker AC-300, or Bruker AM-400 spectrometer. All chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane using the δ scale. ^{1}H NMR spectral data are reported in the order: chemical shift, multiplicity, (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad), coupling constant (J) in Hertz, and number of protons. Chemical ionization mass spectra MS(CI) were obtained using a Finnigan 4023 quadrupole GC-MS 4500 spectrometer with a source temperature of 140 °C and a pressure of 0.7 torr. Electron impact mass spectra MS(EI) were obtained using a Varian MAT311 spectrometer with an ionization potential of 70 eV. High resolution mass spectra were obtained using a Kratos MS-50 RF spectrometer. X-ray crystallographic data were collected using a Rigaku AFC6R and Siemens P4 diffractometer. Structures were solved using the direct method contained in TEXAN (VAX/VMS) and SHELXTL (Silicon Graphics/UNIX) software package. Elemental analyses were performed by Desert Analytics, Tucson, Arizona.

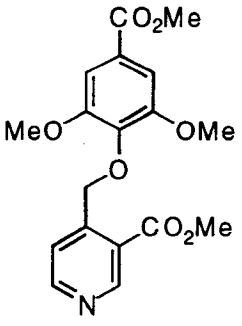
Methyl 3-(Methanesulfonyloxy)methylnicotinate (75). A mixture of **73** (50 mg, 0.74 mmol) and sulfuric acid (24 μL, 0.45 mmol) in 2.5 mL of methanol was refluxed for 10 h. The mixture was cooled to ice bath temperature, solid sodium bicarbonate (50 mg, 1.3 equiv. to H_2SO_4) was added, and the mixture was stirred for 15 min. Methanol was removed in vacuo and the residue was diluted with methylene



chloride. The deposited solid was filtered through a Celite pad and concentrated to give 58 mg of a 1:1 mixture of **74** and **73** based on ^{1}H NMR analysis.

The crude mixture was dissolved in 2 mL of methylene chloride containing triethylamine (40.3 μL, 0.29 mmol) and was treated with methanesulfonyl chloride (16.3 μL, 0.21 mmol) at 0 °C. After 30 min a few drops of methanol and a small quantity of silica gel was added and the volatile material was evaporated. Column chromatography of the absorbed silica gel (hexane-ethyl acetate, 5:1 to 2:1) afforded 41 mg (93% based on recovered starting material) of **75**: IR (film) 1722, 1356, 1292, 1175, 1115, 991, 964, 845, 813 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.81 (d, J=5.0 Hz, 1H), 7.64 (d, J=5.0 Hz, 1H), 5.72 (s, 2H), 4.05 (s, 3H), 3.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 153.6, 151.7, 145.6, 122.5, 121.0, 68.0, 52.5, 37.7; MS (EI) *m/z* (rel. intensity) 166 (70), 150 (20), 134 (100), 120 (5), 106 (27), 92 (11). This was used immediately for the next reaction due to its instability

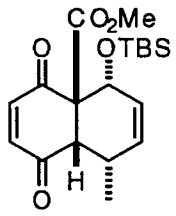
Dimethyl Cathate (69). To a stirred suspension of sodium hydride (4.8 mg, 60%, 0.120 mmol) in 1 mL of acetonitrile was added methyl syringate (25.7 mg, 0.120 mmol) at room temperature. After the evolution of hydrogen was complete, a solution of **75** (20 mg, 0.082 mmol) in 0.5 mL of acetonitrile and 0.5 mL of dimethyl formamide was added. After 17 h at room temperature the mixture was refluxed for 1 h and cooled to room temperature. Water was added and the mixture was extracted with methylene chloride (2 X 10 mL). The separated organic layer was washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue (methylene chloride to hexane-ethyl acetate,



1:2) afforded 22 mg (74%) of **69** as a colorless solid: mp 163 - 164 °C (lit.[20] 162 - 162.5 °C); IR (KBr) 1721, 1592, 1412, 1341, 1290, 1227, 1218, 1132, 1113 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.78 (d, J=5.0 Hz, 1H), 8.09 (d, J=5.0 Hz, 1H), 7.31 (s, 2H), 5.48 (s, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 3.87 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 166.0, 153.1, 152.9, 151.2, 150.3, 140.8, 125.6, 122.4, 121.5, 106.6, 71.7, 56.1, 52.2; MS(EI) *m/z* (rel. intensity) 361 (M^+, 2), 330 (7), 211 (29), 196 (1), 183 (5), 179 (2), 151 (33), 150 (100), 140 (2), 135 (2), 134 (2), 125 (6), 124 (3), 120 (8), 109 (3); HRMS *m/z* Calcd for $C_{18}H_{19}O_7N$ (M + 1):361.1156. Found: 361.1161.

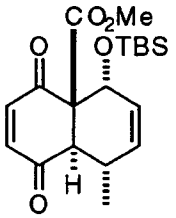
(E,E)-1-(*t*-Butyldimethylsilyl)oxypenta-1,3-diene (81). To a stirred solution of *trans* 2-pentenal (10 g, 118.8 mmol) and triethylamine (24.8 mL, 142.6 mmol) in 200 mL of methylene chloride was added dropwise *t*-butyldimethylsilyl triflate (26.4 mL, 115.2 mmol) at 0 °C. After the addition was complete, the mixture was refluxed for 4 h. To the resulting mixture was added aqueous sodium bicarbonate solution and the organic layer was separated. The separated organic layer was washed with saturated brine, dried and concentrated in vacuo. Vacuum distillation (1 mm Hg, 100 - 110 °C) of the residue afforded 17.6 g (89%) of a mixture of stereoisomeric 1-*t*-butyldimethylsilyl)oxypenta-1,3-dienes which contained 25~30% of the (E, E) isomer.

Methyl (4aβ,5α,8α,8aβ)-1,5,8,8a-Tetrahydro-5-(*t*-butyldimethylsilyl)oxy-1,4-dioxo-8-methyl-4a(4H)-naphthalenecarboxylate (79). To a stirred solution of



methyl gentisate (**82**, 4.28 g, 25.5 mmol) and 1-*t*-butyldimethylsilyloxypenta-1,3-diene (16 g, 80.6 mmol, mixture of stereoisomers) in 24 mL of toluene at 10 °C was added silver (I) oxide (11.8 g, 50.9 mmol) in one portion. The mixture was warmed to room temperature and stirred for 19 h, then was diluted with diethyl ether (100 mL) and filtered through Celite. The Celite was washed thoroughly with diethyl ether and the filtrate was concentrated in vacuo. The residue was purified by chromatography (hexane-ethyl acetate, 6=1) to give 8.2 g (88%) of **79** as a yellowish solid: m.p. 57° - 59 °C; IR (film) 1749, 1710, 1686, 1253, 1227, 1089, 1058, 1037, 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, J=10.3 Hz, 1H), 6.57 (d, J=10.3 Hz, 1H), 5.68 (m, 1H), 4.77 (m, 1H), 3.76 (s, 3H), 3.64 (d, J=4.7 Hz, 1H), 2.17 (m, 1H), 1.42 (d, J=7.5 Hz, 3H), 0.73 (s, 9H), 0.01 (s, 3H), -0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 169.1, 144.3, 138.4, 132.7, 125.8, 67.1, 66.2, 53.0, 50.4, 30.0, 25.5, 17.7, 17.1, -4.6, -5.2; MS (CI) *m/z* (rel. intensity) 365 (M + 1, 100), 349 (43), 307 (65); HRMS *m/z* Calcd for $C_{19}H_{29}O_5Si$: 365.1784. Found: 365.1786.; Anal. Calcd for $C_{19}H_{28}O_5Si$: C, 62.59; H, 7.76. Found: C, 62.79; H, 7.67.

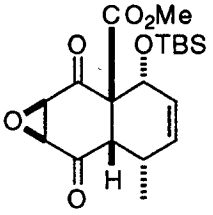
Methyl (4aβ,5α,8α,8aα)-1,5,8,8a-Tetrahydro-5-(*t*-butyldimethylsilyl)oxy-1,4-dioxo-8-methyl-4a(4H)-naphthalenecarboxylate (83). A mixture of **79** (117



mg, 0.321 mmol) and neutral alumina (3 g, Brockman, activity 1, 80-100 mesh) in 8 mL of benzene was stirred for 4 h at room temperature. The resulting mixture was filtered through Celite and the Celite was washed with ethyl acetate (20 mL). Concentration of the filtrate afforded 113 mg (99%) of **83** as a

viscous oil (trans:cis > 30:1 based on ^{1}H NMR analysis): IR (film) 1748, 1733, 1697, 1273, 1252, 1212, 1180, 1073, 1047, 1009, 991, 864, 850, 839, 779 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, J=10.2 Hz, 1H), 6.57 (d, J=10.2 Hz, 1H), 5.79 (m, 1H), 5.62 (dd, J=9.9, 2.9 Hz, 1H), 4.99 (d, J=5.6 Hz, 1H), 3.58 (s, 3H), 3.32 (d, J=9.9 Hz, 1H), 2.82 (m, 1H), 1.19 (d, J=6.8 Hz, 1H), 0.79 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 191.6, 167.1, 142.6, 137.5, 136.2, 125.7, 68.0, 65.1, 53.0, 50.3, 29.9, 25.6, 20.7, 17.8, -4.0, -5.0; MS (CI) *m/z* (rel. intensity) 365 (M + 1, 26), 363 (5), 351 (3), 350 (8), 349 (34), 308 (8), 307 (44), 234 (14), 233 (100); HRMS *m/z* Calcd for $C_{19}H_{28}O_5Si$ (M + 1): 365.1784. Found: 365.1785.

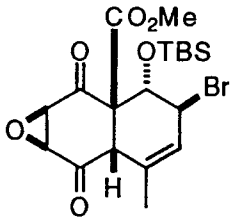
Methyl (2β,3β,4aβ,5α,8α,8aβ)-1,2,3,5,8,8a-Hexahydro-5-(*t*-butyldimethylsilyl)oxy-1,4-dioxo-8-methyl-4a(4H)-2,3-epoxynaphthalenecarboxylate (84).



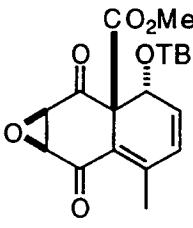
To a stirred solution of **79** (650 mg, 1.72 mmol) and 70% *t*-butyl hydrogen peroxide (1.2 mL, 8.76 mmol) in 10 mL of tetrahydrofuran was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (257 μL, 1.72 mmol) in three portions over 5 min at 0 °C. After 20 min at this temperature the mixture was passed through a pad of neutral alumina (hexane-ethyl acetate, 5:1) and the eluent was concentrated in vacuo. Column chromatography (hexane-ethyl acetate, 8:1) of the residue afforded 604 mg (89%) of **84** as a colorless solid: IR (film) 1750, 1741, 1720, 1260, 1248, 1231, 1054, 1032, 854, 838 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (br.d, J=10.3 Hz, 1H), 5.63 (m, 1H), 4.68 (m, 1H), 3.99 (d, J=4.6 Hz, 1H), 3.75 (s, 3H), 3.66 (d, J=4 Hz, 1H), 3.57 (d, J=4.0 Hz, 1H), 2.09 (m, 1H), 1.29 (d, J=7.5 Hz, 3H), 0.80 (s, 9H), 0.31 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 198.0, 168.1, 133.3, 124.7, 68.1, 65.6, 61.5, 56.8, 53.1, 41.8, 28.4, 25.53, 25.47, 17.8, 17.1, -4.5, -5.2; MS (CI) *m/z* (rel. intensity)

381 (M + 1,44), 365 (68), 323 (100), 249 (87), 211 (17), 189 (31), 177 (87); HRMS *m/z* Calcd for $C_{19}H_{28}O_6Si$ (M + 1): 380.1655. Found: 380.1655.

Methyl (2β,3β,4aβ,5α,8aβ)-1,2,3,5,6,8a-Hexahydro-6-bromo-5-(*t*-butyldimethylsilyl)oxy-8-methyl-1,4-dioxo-4a(4H)-2,3-epoxynaphthalenecarboxylate (86). A mixture of **84** (100 mg, 0.253 mmol), N-bromosuccinimide (50 mg, 0.279 mmol), and a catalytic amount of benzoyl peroxide (≈1 mg) in 3 mL of carbon tetrachloride was refluxed for 1.5 h. The mixture was cooled to room temperature and was concentrated in vacuo. Column chromatography (hexane-ethyl acetate, 6:1) of the residue afforded 114 mg (94%) of **86** as a colorless solid: IR (film) 1735, 1725, 1252, 1235, 1069, 861, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (m, 1H), 5.04 (s, 1H), 4.60 (s, 1H), 4.43 (m, 1H), 3.78 (s, 3H), 3.70 (d, J=4.2 Hz, 1H), 3.6~3.7 (1H), 1.90 (d, J=1.3 Hz, 3H), 0.76 (s, 9H), 0.09 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 196.4, 165.2, 133.8, 121.7, 63.1, 56.5, 53.2, 46.0, 44.6, 25.3, 23.7, 17.6, -4.6, -5.5; MS (CI) *m/z* (rel. intensity) 458 (M + 1, 100), 407 (13), 379 (34), 377 (39), 321 (16), 299 (23), 297 (21); HRMS Calcd for $C_{19}H_{27}O_6SiBr$ (M + 1): 458.0760. Found: 458.0760.

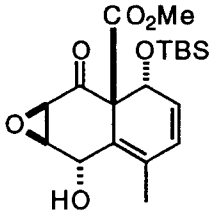


Methyl (2β, 3β, 4aβ, 5α)-1,2,3,5-Tetrahydro-5-(*t*-butyldimethylsilyl)oxy-1,4-dioxo-8-methyl-4a(4H)-2,3-epoxynaphthalenecarboxylate (87). To a stirred solution of **86** (47 mg, 0.10 mmol) in 2 mL of methylene chloride was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (23 μL,0.15 mmol) dropwise at 0 °C. After 1 h an additional quantity of DBU (23 μL) was added and stirring was continued for 1 h. The mixture was filtered through a short pad of silica



gel with ethyl acetate and the filtrate was concentrated in vacuo. Column chromatography of the residue (hexane-ethyl acetate, 6:1) afforded 19 mg (49%) of **87** as an oil and 6 mg (13%) of recovered **86**. Spectroscopic data for **87**: IR (film) 1738, 1675, 1549, 1253, 1084, 857, 839 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.17 (dd, J=9.4, 5.3 Hz, 1H), 6.11 (d, J=9.1 Hz, 1H), 4.66 (dd, J=4.9, 0.9 Hz, 1H), 3.78 (d, J=4.4 Hz, 1H), 3.75 (d, J=4.4 Hz, 1H), 3.71 (s, 3H), 2.40 (s, 3H), 0.73 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 190.5, 166.2, 151.5, 134.1, 131.7, 121.7, 64.9, 63.2, 60.0, 59.1, 53.6, 25.6, 21.7, 17.8, -4.5, -4.8.

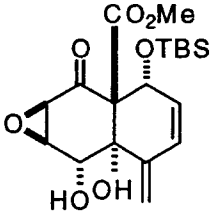
Methyl (1α,2β,3β,4aβ,5α)-1,2,3,5-Tetrahydro-5-(*t*-butyldimethylsilyl)oxy-1-hydroxy-8-methyl-4-oxo-4a(4H)-2,3-epoxynaphthalenecarboxylate (78). To



a stirred solution of **87** (19 mg, 0.050 mmol) and cerium chloride heptahydrate (0.4 M in MeOH, 137 μL, 0.055 mmol) in 1 mL of methanol was added dropwise a solution of sodium borohydride (0.5 M in diglyme, 110 μL, 0.055 mmol) at 0 °C. After the addition was complete, the mixture was allowed to warm to room temperature and stirred for 5 min. A few drops of acetone was added to destroy residual sodium borohydride and the mixture was diluted with water and ethyl acetate (5 mL). The organic layer was separated and was washed with saturated brine, dried, and concentrated in vacuo to give 17 mg (90%) of **78**: IR (film) 3450, 1742, 1725, 1251, 1232, 1211, 1198, 1078, 1011, 859, 837, 778, 609 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (d, J=3.2 Hz, 1H), 4.95 (dd, J=10.7, 3.5 Hz, 1H), 4.77 (m, 1H), 3.87 (dd, J=3.8 Hz, 1H), 3.71 (s, 3H), 3.56 (d, J=3.8 Hz, 1H), 2.90 (d, J=10.7 Hz, 1H, OH), 2.06 (s, 3H), 0.76 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 168.1, 136.5, 132.0, 126.4, 126.0, 65.9, 64.8, 63.3, 60.2, 58.0, 53.7, 25.7, 18.3, 17.9,

-4.4, -4.8; MS(CI) *m/z* (rel. intensity) 381 (M + 1, 10), 363 (100), 323 (22), 305 (12), 249 (55), 231 (15), 207 (12), 189 (9), 173 (28), 147 (60), 133 (35), 117 (45), 99 (40); HRMS *m/z* Calcd for $C_{19}H_{29}O_6Si$ (M + 1): 381.1725. Found: 381.1740.

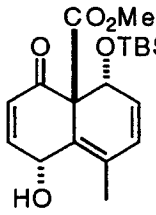
Methyl (1α,2β,3β,4aβ,5α,8aα)-1,2,3,5,8,8a-Hexahydro-5-(*t*-butyldimethylsilyl)oxy-1,8a-dihydroxy-8-methylene-4-oxo-4a(4H)-2,3-epoxynaphthalene-carboxylate (90). A mixture of **68** (30 mg, 0.080 mmol) and 6 mg of rose bengal in 5 mL of methylene chloride was irradiated with a sunlamp for 22 h at room temperature. The mixture was concentrated in vacuo and the residue was passed through a short pad of silica gel (hexane-ethyl acetate, 4:1) to give 5.6 mg of **89**.



Hydroperoxide **89** was treated with an excess of triphenylphosphine in ethyl acetate (3 mL) for 12 h at room temperature. The mixture was concentrated in vacuo and the residue was purified by column chromatography (hexane-ethyl acetate, 4:1) to give 5.5 mg (28%) of **90**: IR (film) 3397, 3381, 1744, 1721, 1253, 1236, 1185, 1077, 1035, 1006, 852, 842 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 6.36 (d, J=9.8 Hz, 1H), 6.13 (s, 1H), 5.80 (dd, J=9.8, 6.0 Hz, 1H), 5.70 (d, J=1.2 Hz, 1H), 5.59 (s, 1H), 4.89 (d, J=6.0 Hz, 1H), 4.44 (d, J=11.5 Hz, 1H), 4.30 (dd, J=11.5, 4.1 Hz, 1H), 3.93 (d, J=4.0 Hz, 1H), 3.70 (s, 3H), 3.64 (d, J=4.0 Hz, 1H), 0.82 (s, 9H), 0.24 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 168.5, 141.4, 134.5, 123.3, 122.0, 77.6, 69.2, 67.4, 62.6, 60.0, 58.5, 53.7, 25.6, 17.8, -4.4, -5.2; MS(CI) *m/z* (rel. intensity) 397 (M + 1, 5), 381 (3), 365 (2), 349 (7), 339 (4), 307 (8), 293 (6), 266 (15), 265 (100), 189 (13), 187 (12), 177 (32), 161 (18), 159 (14), 133 (32); HRMS *m/z* Calcd for $C_{19}H_{29}O_7Si$ (M + 1): 397.1682. Found: 397.1683.

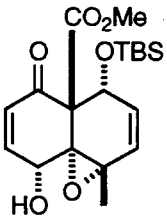
Methyl (4aβ, 5α)-1,5-Dihydro-5-(*t*-butyldimethylsilyl)oxy-8-methyl-1,4-dioxo-4a(4H)-naphthalene carboxylate (93). A solution of **79** (7.51 g, 20.6 mmol), N-bromosuccinimide (3.86 g, 21.7 mmol) and a catalytic amount of benzoyl peroxide in 140 mL of carbon tetrachloride was refluxed for 3 h. To the mixture was added 8 mL of triethylamine and reflux was continued for an additional 2 h. The mixture was cooled to room temperature and poured into aqueous saturated sodium bicarbonate solution (100 mL). The resulting mixture was extracted with methylene chloride (150 mL) and the separated organic layer was dried and concentrated in vacuo. Column chromatography (hexane-ethyl acetate, 5:1) of the residue afforded 7.29 g (98%) of **93** which slowly solidified in the refrigerator to give a yellow solid: IR (film) 1745, 1685, 1661, 1559, 1074, 839 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 6.89 (d, J=10.1 Hz, 1H), 6.68 (d, J=10.1 Hz, 1H), 6.32 (dd, J=5.5, 9.6 Hz, 1H), 6.05 (d, J=9.6 Hz, 1H), 5.06 (d, J=5.5 Hz, 1H), 3.59 (s, 3H), 2.32 (s, 3H), 0.74 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 186.6, 166.8, 145.0, 144.3, 137.1, 133.4, 131.4, 122.9, 65.8, 63.8, 53.3, 25.5, 20.7, 17.8, -4.0, -5.1; MS (CI) *m/z* (rel. intensity) 363 (M + 1, 53), 347 (28), 305 (24), 231 (100), 198 (15), 170 (96); HRMS *m/z* Calcd for $C_{19}H_{27}O_5Si$ (M + 1): 363.1627. Found: 363.1627.

Methyl (1α,4aβ,5α)-1,5-Dihydro-5-(*t*-butyldimethylsilyl)oxy-1-hydroxy-8-methyl-4-oxo-4a(4H)-naphthalenecarboxylate (94). To a stirred solution of



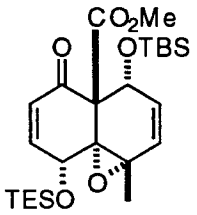
93 (7.29 g, 20.1 mmol) and cerium chloride hexahydrate (7.84 g, 22.1 mmol) in 1.4 L of methanol was added solid sodium borohydride (0.76 g, 20.1 mmol) portionwise during 30 min at 0 °C. After the addition was complete, the mixture was warmed to room temperature and stirring was continued for 30 min. Acetone (5 mL) was added to destroy residual sodium borhydride and the volatile material was evaporated in vacuo. The residue was diluted with methylene chloride (150 mL) and washed with water (200 mL). The separated aqueous layer was extracted with methylene chloride (50 mL X 2) and the combined organic layer was washed with saturated brine, dried, and concentrated in vacuo to give crude **94** (6.6 g, 90%) which was used in the next step without further purification. A pure sample of **94** was obtained by column chromatography (hexane-ethyl acetate, 5:1): IR (KBr) 3463, 1727, 1663, 1466, 1440, 1253, 1224, 1099, 839 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (dd, J=4, 10.3 Hz, 1H), 6.14 (dd, J=1.5, 10.3 Hz, 1H), 6.00 (dd, J=5.4, 9.4 Hz, 1H), 5.85 (d, J=9.4 Hz, 1H), 5.20 (br. d, J=11.6 Hz, 1H), 3.60 (s, 3H), 2.07 (d, J=1.3 Hz, 3H), 0.76 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0, 168.0, 149.3, 133.8, 131.1, 127.9, 127.5, 126.5, 65.8, 64.1, 53.1, 25.7, 19.8, 17.9, -4.1, -5.1; MS (CI) *m/z* (rel. intensity) 365 (M + 1, 12), 349 (39), 347 (86), 331 (24), 317 (20), 289 (22), 275 (15), 235 (20), 233 (100), 201 (75), 175 (30), 173 (70); HRMS *m/z* Calcd for $C_{19}H_{29}O_5Si$ (M + 1): 365.1776. Found: 365.1783.

Methyl (1α,4aβ,5α,8a,8aα)-1,5-Dihydro-5-(*t*-butyldimethylsilyl)oxy-1-hydroxy-8(β)-methyl-4-oxo-4a(4H)-8,8a-epoxynaphthalenecarboxylate (91).

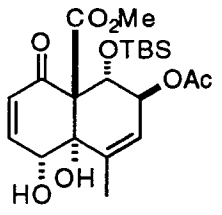


To a stirred solution of crude **94** (6.6 g) in 400 mL of methylene chloride and 800 mL of aqueous phosphate buffer (pH 8) was added *m*-chloroperbenzoic acid (6.0 g, 60.2 mmol) portionwise at 0 °C. After the addition was complete, the mixture was warmed to room temperature and stirred for 50 min. Excess dimethyl sulfide was added to remove residual *m*-chloroperbenzoic acid and stirring was continued for 15 min. The organic layer was separated and concentrated in vacuo. Column chromatography (hexane-ethyl acetate, 4:1) of the residue gave 5.19 g (68% based on **93**) of **91** as a colorless solid: mp 89.5 - 90.5 °C; IR (film) 3487, 1731, 1691, 1253, 1213, 1109, 1091, 1046, 840, 813 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (dd, J=10.5, 2.4 Hz, 1H), 6.10 (dd, J=10.5, 2.2 Hz, 1H), 5.96 (m, 2H), 5.11 (m, 2H), 3.66 (s, 3H), 2.71 (d, J=9.9 Hz, 1H, OH), 1.76 (s, 3H), 0.79 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.9, 167.2, 152.2, 134.4, 132.1, 127.2, 67.7, 67.5, 63.0 (two peaks), 58.3, 53.3, 25.6, 17.8, 17, -4.0, -5.0; MS (CI) *m/z* (rel. intensity) 381 (M + 1, 100), 365 (98), 323 (79), 331 (33), 277 (10), 249 (80), 217 (22); HRMS *m/z* Calcd for $C_{19}H_{29}O_6Si$ (M + 1): 381.1725. Found: 381.1732.; Anal. Calcd for $C_{19}H_{28}O_6Si$: C, 59.96; H, 7.43. Found: C, 59.63; H, 7.54.

Methyl (1α,4aβ,5α,8a,8aα)-1,5-Dihydro-5-(*t*-butyldimethylsilyl)oxy-1-(triethylsilyl)oxy-8(β)-methyl-4-oxo-4a(4H)-8,8a-epoxynaphthalenecarboxylate (106). To a stirred solution of triethylamine (14 μL, 0.098 mmol) and **91** (26 mg, 0.066 mmol) in 0.5 mL of methylene chloride was added triethylsilyltrifluoromethansulfonate (18 μL, 0.078 mmol) at 0 °C. After 45 min the mixture was purified by a short column of silica gel (hexane-ethyl acetate, 2:1) to give 30 mg (99%) of **106** as a colorless solid: IR (film) 1687, 1253, 1209, 837, 774, 739, 723 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 6.87 (d, J=10.4 Hz, 1H), 6.08 (dd, J=10.4, 2.1 Hz, 1H), 5.92 (m, 2H), 5.52 (s, 1H), 5.05 (d, J=5.9 Hz, 1H), 3.66 (s, 3H), 1.76 (s, 3H), 0.98 (t, J=8.0 Hz, 9H), 0.79 (s, 9H), 0.69 (m, 6H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.9, 167.6, 153.8, 136.0, 131.2, 127.8, 68.6, 68.5, 66.1, 63.9, 58.0, 53.1, 25.6, 17.8, 6.9, 5.4, -3.9, -5.1; MS (CI) *m/z* (rel. intensity) 494 (M + 1, 30), 479 (25), 437 (95), 433 (45), 419 (20), 409 (20), 405 (62), 377 (33), 363 (20), 339 (32), 331 (35), 305 (40), 303 (100), 279 (63), 217 (38), 203 (24), 199 (20), 189 (24), 185 (25), 153 (20), 125 (20); HRMS *m/z* Calcd. for $C_{25}H_{42}O_6Si_2$ (M + 1): 494.2520. Found: 494.2520.

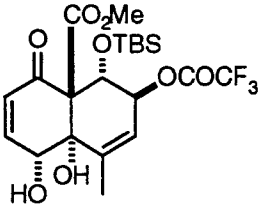


Methyl (1α,4aβ,5α,6β,8aα)-1,5,6,8a-Tetrahydro-6-acetoxy-5-(*t*-butyldimethylsilyl)oxy-1,8a-dihydroxy-8-methyl-4a(4H)-naphthalenecarboxylate (95). A solution of **91** (145 mg, 0.3810 mmol) in 2 mL of acetic acid was refluxed for 5 h. The mixture was cooled to room temperature and the volatile material was removed in vacuo. Column chromatogrphy (hexane-ethyl aceate, 3:1) of the residue afforded 119 mg (71%) of **95** as a colorless oil: IR (film) 3421, 3399, 1737, 1701, 1371, 1251, 1226, 1031, 838, 784 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 6.66 (dd, J=10.5, 2.5 Hz, 1H), 6.00 (dd, J=10.5, 1.8 Hz,



1H), 5.46 (m, 1H), 5.39 (s, 1H, OH), 5.16~5.07 (m, 2H), 4.87 (t, J=1.7 Hz, 1H), 3.62 (s, 3H), 3.18 (d, J=11.7 Hz, 1H, OH), 2.14 (br. s, 3H), 2.00 (s, 3H), 0.85 (s, 3H), 0.31 (s, 3H), 0.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1, 169.6, 166.8, 149.2, 144.8, 126.5, 117.9, 75.3, 71.0, 69.2, 68.7, 63.7, 52.7, 25.7, 21.4, 20.9, 17.9, -4.9, -5.3; MS (CI) *m/z* (rel. intensity) 441 (M+ 1, 24), 425 (31), 424 (25), 422 (100), 407 (14), 383 (35), 382 (24), 381 (99), 367 (12), 365 (32), 364 (18), 363 (70), 323 (27), 249 (11), 231 (15); HRMS *m/z* Calcd for $C_{21}H_{32}O_8Si$ (M + 1): 441.1944. Found: 441.1944.

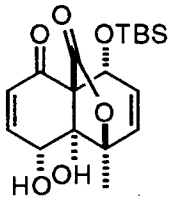
Methyl (1α,4aβ,5α,6β,8aα)-1,5,6,8a-Tetrahydro-5-(*t*-butyldimethylsilyl)oxy-1,8a-dihydroxy-8-methyl-4-oxo-6-trifluoroacetoxy-4a(4H)-naphthalenecarboxylate (96). A solution of **91** (24.4 mg, 0.0641 mmol) in 0.2 mL of trifluoroacetic acid was stirred for 2 h at room temperature. The resulting mixture was diluted with diethyl ether (10 mL) and washed with aqueous sodium bicarbonate solution. The separated organic layer was washed with brine, dried and concentrated in vacuo. Column chromatography (hexane-ethyl acetate, 3:1 to 2:1) of the residue afforded 6.5 mg (33%) of **96** and 10 mg (67%) of **97**. Spectroscopic data for **97**: IR (film) 3425, 1785, 1745, 1697, 1378, 1252, 1221, 1172, 1149, 1095, 1031, 925 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.73 (dd, J=10.5, 2.7 Hz, 1H), 6.09 (dd, J=10.5, 1.8 Hz, 1H), 5.61 (m, 1H), 5.44 (m, 1H), 5.12 (dt, J=14.4, 1.1 Hz, 1H), 4.95 (m, 1H), 4.46 (d, J=1.0 Hz, 1H, OH), 3.78 (d, J=4.5 HZ, 1H, OH), 3.62 (s, 3H), 3.15 (d, J=11.7 Hz, 1H, OH), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.8, 165.9, 150.1, 146.5, 126.3, 116.4, 116.1, 75.7, 72.4, 69.9, 68.5, 63.9, 53.7, 52.9, 52.8, 21.3; MS (CI) *m/z* (rel. intensity) 381 (M + 1, 6), 379 (2), 363 (14), 345 (3), 313 (1), 301 (2), 295 (2), 268 (15), 267 (100), 250 (11), 249 (71), 231 (14), 221 (18), 217



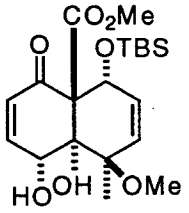
(29), 189 (14), 115 (63); HRMS *m/z* Calcd for $C_{15}H_{16}F_3O_8$ (M + 1): 381.0797. Found: 381.0797.

Spectroscopic data for **96**: IR (film) 3416, 1784, 1745, 1703, 1375, 1253, 1223, 1176, 1145, 1101, 1026, 1032, 935, 837, 785 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.68 (dd, J=10.4, 2.7 Hz, 1H), 6.03 (dd, J=10.4, 1.7 Hz, 1H), 5.49 (m, 1H), 5.29 (m, 2H), 5.11 (br. d, J=11.7 Hz, 1H), 4.94 (t, J=1.7 Hz, 1H), 3.59 (s, 3H), 3.16 (d, J=11.7 Hz, 1H, OH), 2.18 (t, J=1.8 Hz, 3H), 0.86 (s, 9H), 0.32 (s, 3H), 0.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.6, 166.1, 149.3, 147.7, 126.4, 115.5, 75.0, 73.2, 70.5, 68.6, 63.6, 53.0, 25.7, 21.5, 17.9, -5.0, -5.2; MS (CI) *m/z* (rel. intensity) 495 (M + 1, 20), 479 (17), 478 (11), 477 (40), 437 (16), 383 (14), 382 (30), 381 (M - CF_3CO_2, 100), 365 (13), 363 (35), 249 (20), 115 (38); HRMS *m/z* Calcd for $C_{21}H_{30}F_3O_8Si$ (M + 1): 495.1662. Found: 495.1662.

Lactone 102. A mixture of **91** (7 mg, 0.0184 mmol) and pyridium *p*-toluenesulfonate (4 mg, 0.016 mmol) in reagent grade acetone (1 mL) was stirred for 24 h at room temperature. The mixture was concentrated in vacuo and was purified by column chromatography (hexane-ethyl acetate, 2:1) to give 4 mg (57%) of **102** as a colorless solid: IR (film) 3390, 1777, 1692, 1385, 1257, 1228, 1202, 1081, 1054, 1001, 905, 843, 787 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.98 (dd, J=10.5, 1.8 Hz, 1H), 6.15 (dd, J=10.5, 2.3 Hz, 1H), 6.03 (m, 2 H), 5.76 (s, 1H, OH), 5.04 (m, 1H), 4.69 (dt, J=11.4, 2.1 Hz, 1H), 3.22 (d, J=11.4 Hz, 1H), 1.69 (s, 3H), 0.82 (s, 9H), 0.20 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.8, 167.1, 152.8, 134.6, 130.8, 128.0, 83.6, 81.8, 67.6, 65.3, 60.5, 26.9, 25.4, 18.2, 17.7, -4.6, -5.5; MS (CI) *m/z* (rel. intensity) 367 (M + 1, 100), 351 (11), 235 (22), 191 (27); HRMS *m/z* Calcd for $C_{18}H_{27}O_6Si$ (M + 1): 367.1569. Found: 367.1575.

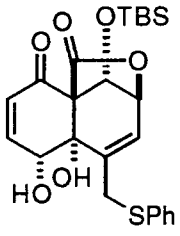


Methyl (1α,4aβ,5α,8S*)-1,5,8,8a-Tetrahydro-5-(*t*-butyldimethylsilyl)-oxy-1,8a-dihydroxy-8-methoxy-8-methyl-4a(4H)-naphthalenecarboxylate (103).



A solution of **91** (37 mg, 0.0972 mmol) in 0.5 mL of methanol containing a catalytic amount of pyridinium *p*-toluenesulfonate was stirred for 20 h at room temperature. The mixture was concentrated in vacuo and was purified by column chromatography (hexane-ethyl acetate, 3:1) to give 10 mg (25%) of slightly impure **103**. A pure sample of **103** was obtained as a colorless solid by recrystalization from hexane-diethyl ether: IR (film) 3548, 3405, 1682, 1386, 1257, 1189, 1157, 1128, 1071, 1034, 1010, 939, 914, 838, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.78 (dd, J=10.0, 1.7 Hz, 1H), 6.06 (dd, J=10.0, 2.3 Hz, 1H), 5.99 (dd, J=9.6, 4.2 Hz, 1H), 5.82 (d, J=9.5 Hz, 1H), 5.79 (s, 1H), 4.88 (d, J=4.1 Hz, 1H), 4.66 (dt, J=11.4, 2.1 Hz, 1H), 3.32 (s, 3H), 3.21 (s, 3H), 3.16 (d, J=11.6 Hz, 1H), 1.50 (s, 3H), 0.79 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 182.3, 152.8, 133.8, 130.2, 129.0, 116.2, 81.4, 81.3, 68.8, 66.7, 62.1, 52.0, 49.0, 25.6, 19.5, 17.7, -4.3, -5.5; MS (CI) *m/z* (rel. intensity) 413 (M + 1, 21), 395 (16), 383 (8), 382 (23), 381 (92), 323 (14), 309 (14), 307 (21), 305 (12), 282 (20), 281 (100), 280 (15), 277 (12), 265 (15), 263 (13), 261 (13), 249 (50), 231 (19), 219 (15), 191 (28); HRMS *m/z* Calcd for $C_{20}H_{33}O_7Si$ (M + 1): 413.1995. Found: 413.1997.

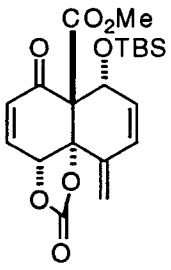
Sulfide 99. To a stirred solution of **91** (9.5 mg, 0.0250 mmol) and thiophenol (7.7 μL, 0.0749 mmol) in 0.5 mL of toluene was added titanium tetraisopropoxide (22.3 μL, 0.0749 mmol) at room temperature. After 7 h the mixture was passed through a short pad of silica gel (hexane-ethyl acetate, 9:1 to 6:1) and the eluent was concentrated in vacuo. Purification by thin layer chromatography



(0.25 mm, hexane-ethyl acetate, 6:1, two fold elution) of the residue to give 4.8 mg (42%) of **99** and 2 mg (21%) of **98**. Spectroscopic data for **99**; IR (film) 3400, 1782, 1691, 1163, 842, 786, 740.cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5H), 6.83 (dd, J=10.5, 2.1 Hz, 1H), 6.30 (dd, J=10.5, 2.1 Hz, 1H), 6.0 (dd, J=6.0, 1.0 Hz, 1H), 5.18 (dd, J=5.0, 1.0 Hz, 1H), 4.71 (br.s, 1H), 4.69 (s, 1H), 4.62 (dd, J=6.0, 5.0 Hz, 1H), 4.01 (dd, J=15.3, 1.4 Hz, 1H), 3.84 (dd, J=15.3, 1.4 Hz, 1H), 0.84 (s, 9 H), 0.20 (s, 3H), 0.16 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1, 168.6, 149.5, 143.5, 135.3, 130.6, 129.0, 128.1, 126.9, 124.5, 76.0, 72.6, 70.4, 69.7, 62.0, 36.6, 25.4, 17.7, -5.1, -5.2; MS (CI) *m/z* (rel. intensity) 475 (M + 1, 34), 457 (29), 439 (10), 413 (30), 397 (16), 396 (28), 395 (92), 383 (10), 371 (31), 344 (22), 343 (100), 325 (17), 305 (19), 299 (35), 226 (25), 224 (24); HRMS *m/z* Calcd for $C_{24}H_{31}O_6Si$ (M + 1): 475.1602. Found: 475.1608.

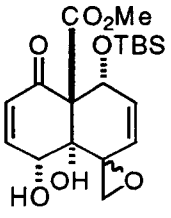
Spectroscopic data for **98**; IR (film) 3541, 3369, 1739, 1688, 1388, 1255, 1229, 1191, 1098, 1060, 1039, 1012, 844, 781 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (dd, J=10.5, 2.1 Hz, 1H), 6.67 (s, 1H, OH), 6.24 (d, J=9.9 Hz, 1H), 6.06 (dd, J=10.5, 1.8 Hz, 1H), 5.98 (s, 1H), 5.92 (dd, J=11.0, 5.7 Hz, 1H), 5.33 (br. d, J=11.0 Hz, 1H), 5.29 (s, 1H), 5.24 (d, J=5.7 Hz, 1H), 3.60 (s, 3H), 0.83 (s, 9H), 0.22 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4, 166.2, 152.0, 143.4, 131.6, 126.3, 125.9, 118.2, 76.0, 69.1, 68.0, 64.7, 53.1, 25.6, 17.8, -4.4, -5.3; MS (CI) *m/z* (rel. intensity) 381 (M + 1, 13), 365 (34), 323 (28), 250 (15), 249 (100), 231 (34), 217 (13), 203 (14), 173 (6); HRMS *m/z* Calcd for $C_{19}H_{29}O_6Si$ (M + 1): 381.1725. Found: 381.1732.

Carbonate 100. A mixture of **98** (18.5 mg, 0.486 mmol) and



carbonyldiimidazole (15.8 mg, 0.972 mmol) in 1.5 mL of toluene was refluxed for 6 h. The mixture was cooled to room temperature and was purified by column chromatography (hexane-ethyl acetate, 6:1 to 2:1) to give 15 mg (76%) of **100** as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6. 81 (dd, J=10.4, 3.0 Hz, 1H), 6.27 (s, 1H), 6.22 (d, J=4.5 Hz, 1H), 6.18 (s, 1H), 6.01 (dd, J=10.2, 4.5 Hz, 1H), 5.86 (d, J=5.4 Hz, 1H), 5.61 (s, 1H), 5.38 (s, 1H), 5.25 (d, J=5.4 Hz, 1H), 3.63 (s, 3H), 0.83 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$,) δ 186.1, 166.0, 152.3, 139.5, 139.1, 129.26, 129.22, 128.5, 117.1, 83.6, 74.2, 65.2, 64.8, 53.8, 25.6, 17.9, -3.9, -5.1; MS (CI) *m/z* 407 (M + 1, 100), 391 (31), 349 (54), 275 (44), 231 (46), 203 (39); HRMS (CI) *m/z* Calcd for $C_{20}H_{27}O_7Si$ (M + 1): 407.1527. Found: 407.1526.; Anal. Calcd for $C_{20}H_{27}O_7Si$: C, 59.09; H, 6.45. Found: C, 59.07; H, 6.38.

Epoxide 101. To a stirred solution of **98** (13 mg, 0.0341 mmol) in 0.5 mL of

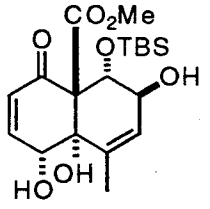


methylene chloride was added *m*-chloroperbenzoic acid (1.5 equiv., 10.7 mg, 0.0512 mmol) at 0 °C. After 0.5 h the mixture was warmed to room temperature and stirring was continued for 7 h. A few drops of dimethylsulfide was added to destroy residual *m*-chloroperbenzoic acid and aqueous sodium bicarbonate solution was added subsequently. After 2 h of vigorous stirring, the mixture was extracted with diethyl ether (10 mL) and the separated organic layer was washed with saturated brine, dried and concentrated in vacuo. Thin layer chromatography (0.25 mm, hexane-ethyl acetate, 3:1) of the residue afforded 6.5 mg of high R_f isomer **101a** and 6.0 mg of lower R_f isomer **101b** in 93% yield. Spectroscopic data for **101a**: IR (film) 3528, 3382, 1738, 1689, 1254,

1229, 1188, 1100, 1058, 1045, 1017, 933, 844, 783 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.74 (dd, J=10.4, 2.2 Hz, 1H), 6.52 (s, 1H), 6.30 (dd, J=10.0, 5.4 Hz, 1H), 6.05 (dd, J=10.4, 1.8 Hz, 1H), 5.37 (d, J=10.0 Hz, 1H), 5.26 (d, J=5.4 Hz, 1H), 4.95 (dt, J=11.9, 2.0 Hz, 1H), 3.93 (d, J=5.3 Hz, 1H), 3.65 (s, 3H), 2.98 (d, J=11.9 Hz, 1H), 2.77 (d, J=5.3 Hz, 1H), 0.83 (s, 9H), 0.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 166.2, 152.0, 131.9, 131.2, 126.2, 75.6, 68.6, 67.9, 64.7, 61.4, 54.6, 53.3, 25.6, 17.8, 14.2, -4.4, -5.3; MS (CI) *m/z* (rel. intensity) 397 (M + 1, 17), 381 (25), 379 (17), 363 (13), 347 (21), 339 (31), 305 (11), 293 (22), 266 (11), 265 (80), 249 (17), 247 (88), 231 (13), 229 (24), 219 (37), 215 (44), 187 (100), 171 (11), 159 (12), 133 (20), 117 (11) ; HRMS Calcd for $C_{19}H_{29}O_7Si$ (M +1): 397.1682. Found: 397.1681.

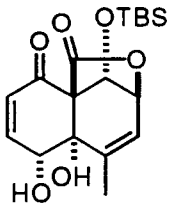
Spectroscopic data for **101b**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.77 (dd, J=10.5, 1.8 Hz, 1H), 6.22 (s, 1H), 6.18 (dd, J=10.2, 1.8 Hz, 1H), 6.04 (dd, J=10.5, 2.2 Hz, 1H), 5.30 (d, J=10.2 Hz, 1H), 5.23 (d, J=5.2 Hz, 1H), 5.13 (br. d, J=6.8 Hz, 1H), 3.63 (s, 3H), 3.57 (d, J=4.2 Hz, 1H), 3.19 (d, J=6.8 Hz, 1H), 2.91 (d, J=4.2 Hz, 1H), 0.82 (s, 9H), 0.19 (s, 6H).

Methyl (1α,4aβ,5α,6β,8aα)-1,5,6,8a-Tetrahydro-5-(*t*-butyldimethylsilyl)oxy-8-methyl-4-oxo-1,6,8a-trihydroxy-4a(4H)-naphthalenecarboxylate (104). A mixture of **91** (62 mg, 0.163 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg, 0.0526 mmol) in 2 mL of acetone was stirred for 30 min at room temperature. The mixture was neutralized by a few drop of triethylamine and was passed through a short pad of silica gel with diethyl ether as eluent. Column chromatography (hexane-ethyl aceate, 3:1 to 2:1) of the concentrated eluent afforded 27 mg of **102** and 16 mg of **104** in 70% yield. Spectroscopic data for **104**: IR (KBr) 3453, 3427, 3381, 1743, 1685, 1466, 1431, 1391, 1258,

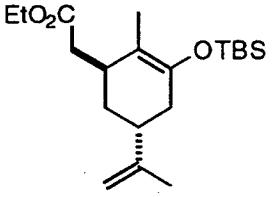


1220, 1174, 1084, 1034, 841, 783 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 6.60 (dd, J=10.3, 2.4 Hz, 1H), 5.99 (d, J=10.3 Hz, 1H), 5.53 (m, 1H), 5.28 (s, 1H, OH), 5.00 (d, J=11.8 Hz, 1H), 4.82 (m, 1H), 4.05 (br. s, 1H), 3.56 (s, 3H), 3.12 (d, J=11.8 Hz, 1H), 2.09 (s, 3H), 1.48 (d, J=4.5 Hz, 1H, OH), 0.81 (s, 9H), 0.25 (s, 3H), 0.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 148.7, 142.7, 126.9, 121.4, 75.5, 73.2, 68.8, 68.4, 63.3, 52.8, 25.7, 21.3, 17.9, -5.0, -5.1; MS (CI) *m/z* (rel. intensity) 399 (M + 1, 23), 383 (29), 382 (22), 381 (100), 363 (65), 341 (28), 305 (20), 249 (23), 231 (22); HRMS *m/z* Calcd for $C_{19}H_{31}O_7Si$ (M + 1): 399.1839. Found: 399.1840.

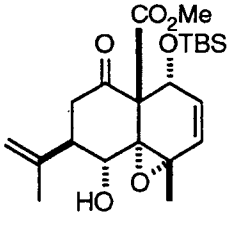
Lactone 105. A mixture of **104** (16 mg, 0.0415 mmol) in 1 mL of toluene was refluxed for 6 h. The mixture was cooled to room temperature and was passed through a short pad of silica gel with hexane-ethyl acetate (4:1) as eluent to give 12.1 mg (84%) of **105** as a colorless solid: IR (film) 3462, 1781, 1691, 1388, 1259, 1164, 1135, 1053, 962, 942, 813, 786.cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 6.79 (dd, J=10.3, 2.1 Hz, 1H), 6.27 (dd, J=10.3, 2.1 Hz, 1H), 5.91 (d, J=5.3 Hz, 1H), 4.62 (dd, J=5.6, 5.3 Hz, 1H), 4.54 (s, 1H, OH), 4.42 (m, 1H), 2.82 (d, J=11.9 Hz, 1H, OH), 2.05 (d, J=1.2 Hz, 3H), 0.87 (s, 9H), 0.22 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 168.9, 149.6, 145.4, 127.9, 122.2, 76.2, 73.0, 70.4, 69.9, 62.1, 25.4, 20.0, 17.7, -5.1.; MS (CI) *m/z* (rel. intensity) 367 (M + 1, 61), 349 (21), 321 (21), 305 (28), 235 (10), 191 (11), 59 (30), 41 (100); HRMS Calcd for $C_{18}H_{27}O_6Si$ (M + 1): 367.1577. Found: 367.1578.; Anal. Calcd for $C_{18}H_{26}O_6Si$: C,58.99; H, 7.16. Found: C,58.61; H, 6.97.



Enol ether 119. To a stirred solution of (*R*)-carvone (50mg, 0.33 mmol) in 2 mL of diethyl ether was added solid mecuric iodide (7.7 mg, 0.017 mmol) and the mixture was stirred at room temperature until the mecuric iodide was dissolved (10 min). The mixture was cooled to -78 °C and ethyl *t*-butyldimethylsilyl ketene acetal (**118**, 100 μL, 0.43 mmol) was added during 15 min. After 2.5 h the mixture was quenched with triethylamine (5μL, 4 equiv. to HgI_2) and was passed through a short pad of silica gel with 5% triethylamine solution in hexane-ethyl acetate (8:1) and the eluent was concentrated in vacuo. Column chromatography (hexane-ethyl acetate, 30:1) of the residue afforded 96 mg (83%) of **119** as a colorless oil: IR (film) 1737, 1255, 1194, 1172, 924, 837, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.73 (br. d, J=5.7Hz, 2H), 4.14 (q, J=7.1Hz, 2H), 1.9-2.2 (6H), 1.73 (s, 3H), 1.61 (s, 3H), 1.26 (t, J=7.1 Hz, 3H), 0.94 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 148.7, 144.2, 113.0, 109.0, 60.2, 38.0, 37.0, 36.3, 35.6, 31.9, 25.8, 20.7, 18.2, 14.6, 14.2, -3.7, -3.9.



Methyl (1α,2β,4aβ,5α,8α,8aα)-1,2,3,5,8,8a-Hexahydro-5-(*t*-butyldimethyl-silyl)oxy-1-hydroxy-8(β)-methyl-2-(1-methyl)ethenyl-4-oxo-4a(4H)-8,8a-epoxynaphthalenecarboxylate (108). To a stirred solution of 2-bromopropene (121 μL, 1.366 mmol) in 4 mL of tetrahydrofuran at -78 °C was added dropwise *t*-butyllithium (1.7 M in pentane, 1.61 mL, 2.732 mmol) via the wall of the flask. After 45 min the resulting pale yellow solution of 2-lithiopropene was immediately transferred via cannula to a suspension of cuprous cyanide in 2 mL of tetrahydrofuran which was cooled to -78 °C. After the transfer was complete, the mixture was allowed to warm slowly by removing

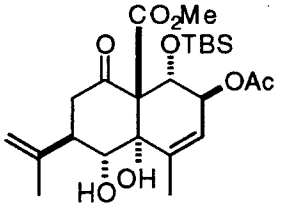


the cooling bath until the solution became homogeneous (3 to 5 min). The mixture was then re-cooled to -78 °C. To the resulting light yellow solution was added slowly via the wall of the flask a solution of trimethylsilyl chloride (1 M in THF, 3.4 mL, 3.416 mmol). Immediately after the addition of trimethylsilyl chloride was complete, a solution of **91** in 1 mL of tetrahydrofuran was added to the yellowish orange solution via cannula and the mixture was stirred for 50 min. Saturated ammonium chloride (4 mL), saturated ammonium hydroxide (4 mL), and diethyl ether (10 mL) were added, the mixture was allowed to warm to ice-bath temperature and stirring was continued until the solution became clear. The organic layer was separated and washed with saturated sodium bicarbonate solution, saturated brine, dried and concentrated to give 50 mg of crude **107**.

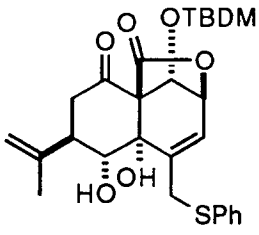
To a stirred solution of crude **107** (50 mg) in 2 mL of methylene chloride was added excess triethylamine-hydrofluoric acid complex at room temperature. The mixture was kept overnight (17 h) and was passed through a short pad of silica gel with diethyl ether (25 mL) as eluent. Column chromatography (hexane-ethyl acetate, 4:1) of the concentrated eluent afforded 30 mg (60%) of **108** as a colorless solid: IR (film) 3509, 1748, 1723, 1250, 1224, 1195, 1098, 1060, 840, 776 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 6. 81 (d, J=9.4 Hz, 1H), 5.88 (dd, J=9.4, 6.0 Hz, 1H), 4.98 (d, J=6.0 Hz, 1H), 4.83 (s, 1H), 4.56 (dd, J=7.7, 6.2 Hz, 1H), 3.61 (s, 3H), 2.73 (m, 3H), 2.55 (d, J=7.7 Hz, 1H, OH), 1.81 (s, 3H), 1.74 (s, 3H), 0.82 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$,) δ 200.6, 167.1, 144.4, 135.4, 131.4, 113.1, 68.7, 68.0, 66.2, 64.7, 59.4, 53..2, 48.3, 42.1, 25.7, 19.9, 17.8, 17.3, -4.0, -5.0; MS (CI) *m/z* (rel. intensity) 407 (M + 1, 100), 409 (6), 408 (16), 407 (59), 406 (23), 405 (79), 392 (10), 391 (38), 389 (36), 387 (22), 381 (14), 375 (15), 374 (9), 373 (26), 366 (17), 365 (69), 363 (13), 357 (14), 348 (11), 347 (41), 333 (15), 331

(19), 323 (12), 319 (17), 315 (11), 309 (15), 292 (13), 291 (75), 279 (10), 277(40), 273 (84), 259 (37), 249 (15), 245 (14), 241 (21), 237 (21), 229 (14), 227 (15), 213 (39), 199 (10), 197 (14), 177(31), 167 (19); HRMS *m/z* Calcd. for $C_{22}H_{35}O_6Si$ (M + 1): 423.2203. Found: 423.2202.; Anal. Calcd for $C_{22}H_{34}O_6Si$: C, 62.53; H, 8.11. Found: C, 62.30; H, 7.98.

Methyl (1α,2β,4aβ,5α,6β,8aα)-1,5,6,8a-Tetrahydro-6-acetoxy-5-(*t*-butyldimethylsilyl)oxy-1,8a-dihydroxy-8-methyl-2-(1-methyl)ethenyl-4-oxo-4a(4H)-naphthalenecarboxylate (109). A solution of **108** (5.2 mg, 0.0123 mmol) in 0.5 mL of acetic acid was heated at 60 - 65 °C for 4 h. The mixture was cooled to room temperature and the volatile material was evaporated in vacuo. Column chromatography (hexane-ethyl acetate, 4:1 to 3:1) of the residue afforded 4.9 mg (78%) of **109**: IR (film) 3541, 3501, 3395, 1736, 1430, 1370, 1231, 1111, 1072, 1018, 839; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.59 (s, 1H, OH), 5.40 (m, 1H), 5.09 (br. d, J=4.9 Hz, 1H), 4.91 (m, 1H), 4.88 (s, 1H), 4.79 (t, J=1.6 Hz, 1H), 4.63 (m, 1H), 3.67 (s, 3H), 2.87 (m, 1H), 2.37 (m, 3H), 2.22 (d, J=10.3 Hz, 1H, OH), 2.16 (s, 3H), 2.00 (s, 3H), 0.88 (s, 9H), 0.32 (s, 3H), 0.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 169.5, 167.3, 146.7, 144.3, 118.1, 113.7, 76.1, 71.6, 70.8, 69.6, 64.5, 52.7, 48.7, 41.5, 25.7, 22.6, 20.9, 18.9, 17.8, -4.9, -5.4; MS (CI) *m/z* (rel. intensity) 483 (M + 1, 24), 465 (38), 449 (23), 425 (19), 424 (29), 423 (100), 409 (7), 408 (10), 407 (37), 406 (14), 405 (45), 391 (17), 389 (15), 365 (17), 333 (22), 273 (99), 257 (10), 255 (14), 237 (11), 142 (24), 123 (18); HRMS *m/z* Calcd. for $C_{24}H_{39}O_8Si$ (M + 1): 483.2414. Found: 483.2412.

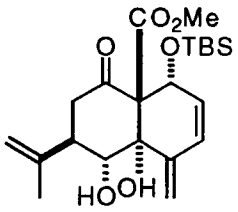


Sulfide 111. To a stirred solution of **108** (27 mg, 0.0639 mmol) and thiophenol



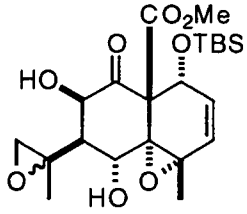
(26 μL, 0.256 mmol) in 1.5 mL of toluene was added neat titanium tetraisopropoxide (76 μL, 0.256 mmol) at room temperature. After standing overnight the mixture was stored for 15 d at -5 °C. The resulting mixture was passed through a short pad of silica gel with diethyl ether as eluent (10 mL) and the opaque filtrate was passed through Celite. The filtrate was concentrated in vacuo and the residue was purified by radial chromatography (1 mm, hexane to hexane-ethyl acetate, 4:1) to give 24.2 mg of **111** as a viscous oil: IR (film) 3446, 1775, 1723, 1259, 1163, 1125, 972, 838, 785 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 5H), 6.17 (dd, J=6.1, 1.0 Hz, 1H), 5.01 (m, 1H), 4.98 (dd, J=4.9, 1.0 Hz, 1H), 4.72 (d, J=1.7 Hz, 1H), 4.59 (dd, J=6.1, 5.9 Hz, 1H), 4.21 (m, 1H), 4.06 (m, 2H), 3.47 (m, 1H), 3.09 (m, 1H), 2.53 (dd, J=15.1, 5.7 Hz, 1H), 2.23 (d, J=6.2 Hz, 1H, OH), 1.86 (s, 3H), 0.85 (s, 9H), 0.23 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 169.6, 145.3, 143.7, 136.0, 129.5, 129.0, 126.3, 124.8, 115.7, 72.3, 71.4, 70.5, 63.5, 47.6, 41.3, 36.3, 25.4, 17.8, 17.7, -5.1, -5.2; MS (CI) *m/z* (rel. intensity) 517 (M + 1, 4), 499 (2), 385 (2), 323 (2), 255 (4), 219 (3), 173 (3), 143 (2), 133 (3), 129 (6), 117 (100); HRMS *m/z* Calcd for $C_{27}H_{37}O_6SSi$ (M + 1): 517.2080. Found: 517.2087.

Methyl (1α,2β,4aβ,5α,8aα)-1,2,3,5,8,8a-Hexahydro-5-(*t*-butyldimethylsilyl)-oxy-1,8a-dihydroxy-8-methylene-2-(1-methyl)ethenyl-4-oxo-4a(4H)-naphthalenecarboxylate (110). To a stirred solution of **108** (5.7 mg, 0.0135 mmol) in



1 mL of toluene was added neat titanium tetraisopropoxide (16 μL, 0.0540 mmol) at room temperature. After 7 h the mixture was passed through a short pad of silca gel with diethyl ether as eluent and the concentrated eluent was purified by column chromatography (hexane-ethyl acetate, 6:1 to 3:1) to give 4.2 mg (74%) of **110**: IR (film) 3356, 3508, 1723, 1467, 1235, 1190, 1044, 1014, 1005, 843, 783 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 6.74 (s, 1H, OH), 6.17 (d, J=10.0 Hz, 1H), 6.11 (s, 1H), 5.82 (dd, J=10.0, 5.6 Hz, 1H), 5.26 (s, 1H), 5.12 (d, J=5.6 Hz, 1H), 4.86 (m, 3H), 3.61 (s, 3H), 2.94 (m, 1H), 2.64 (dd, J=15.3, 13.7 Hz, 1H), 2.35 (m, 2H, 1 proton exchangeable with D_2O), 1.83 (s, 3H), 0.85 (s, 9H), 0.25 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 166.9, 144.5, 144.0, 132.7, 125.4, 119.4, 113.8, 71.1, 68.0, 67.4, 53.2, 48.1, 42.2, 25.7, 18.9, 17.9, -4.5, -5.1; MS (CI) *m/z* (rel. intensity) 423 (M + 1, 17), 407 (31), 405 (11), 389 (5), 366 (7), 365 (30), 331 (7), 319 (20), 293 (9), 292 (18), 291 (100), 274 (11), 273 (61), 259 (10), 213 (10), 177 (44), 133 (24); HRMS, *m/z* Calcd for $C_{22}H_{35}O_6Si$ (M + 1): 423.2203. Found: 423.2202.

Epoxide 112. To a stirred solution of *m*-chloroperbenzoic acid (172 mg, 0.800



mmol) in 5 mL of hexane was added dropwise a solution of **107** (205 mg, 0.3616 mmol) in 5 mL of hexane at 0 °C. After the addition was complete the mixture was warmed to room temperature and stirring was continued for 19 h. The mixture was cooled to 0 °C and the deposited solid was filtered and was washed with pentane (3 mL X 2). The filtrate was concentrated

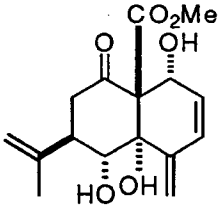
in vacuo and the residue was diluted with methylene chloride (8 mL), then treated with triethylamine-hydrofluoric acid complex (350 mg, 2.9 mmol). After 22 h the mixture was passed through a short pad of silica gel with diethyl ether as eluent, and the concentrated eluent was purified by column chromatography (silica gel 10 g, hexane-ethyl acetate, 2:1 to 3:2) to give 104 mg (64%) of **112** as an epimeric mixture at the terminal epoxide in a 3:1 ratio based on ^{1}H NMR analysis.

Orthoester 113. A mixture of **112** (4.8 mg, 0.0106 mmol) and pyridinium *p*-toluenesulfonate (10 mg, 0.040 mmol) in 1 mL of acetone was stirred for 1.5 h at room temperature. The mixture was passed through a short pad of silica gel with diethyl ether as eluent and the concentrated eluent was purified by column chromatography (hexane-ethyl acetate, 6:1) to give 2.1 mg (48%) of **113** as a colorless solid: mp 141 - 141.5 °C; IR (film) 3500, 1778, 1256, 1197, 1177, 1088, 1045, 1020, 951, 901, 839, 814 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (s, 1H, OH), 5.92 (dd, J=9.5, 4.3 Hz, 1H), 5.80 (d, J=9.5 Hz, 1H), 4.57 (d, J=4.3 Hz, 1H), 4.44 (s, 1H), 4.38 (t, J=10.1 Hz, 1H), 3.34 (s, 3H), 2.94 (d, J=9.9 Hz, 1H, OH), 2.82 (d, J=4.6 Hz, 1H), 2.72 (d, J=4.3 Hz, 1H), 1.51 (s, 3H), 1.47 (s, 3H), 0.88 (s, 9H), 0.27 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 133.8, 129.1, 119.8, 86.1, 84.9, 79.8, 68.3, 65.7, 59.3, 57.7, 56.9, 55.3, 49.8, 25.7, 18.1, 17.8, 17.7, 15.2, -4.5, -5.1; MS (CI) *m/z* (rel. intensity) 455 (M + 1, 80), 439 (12), 437 (25), 423 (34), 421 (12), 405 (11), 379 (12), 365 (15), 363 (15), 351 (27), 324 (15), 323 (86), 322 (18), 302 (63), 287 (15), 277 (19), 273 (19), 247 (30), 229 (42), 201 (34), 167 (46), 60 (100); HRMS *m/z* Calcd for $C_{22}H_{35}O_8Si$ (M + 1): 455.2101. Found: 455.2103.

Compound **113** crystallized from octane in the space group P2(1)/c with a=11.696 (3) Å, b=14.867 (2) Å, c=14.541 (2) Å, β=93.77 (2)°, z=4 and d_{calcd}=1.197 g/cm^3. The intensity data were measured on a Rikagu AFC6R diffractometer (Mo Kα radiation). There were 2168 observed reflections [I>3.00 (I)] and the structure was solved by direct methods. The final discrepancy indices were R=0.066 and Rw=0.095.

Isopropenylmagnesium Bromide. To a suspension of magnesium turnings (1.22 g, 50.5 mmol) cut into small pieces in 80 mL of tetrahydrofuran was added a small amount of 2-bromopropene under sonication. After 2 min the reaction was initiated and 2-bromopropene (3.74 mL, 42.1 mmol) was added at a rate to maintain the reaction mixture at ca 45 °C. After the addition was complete, stirring was continued until the mixture had cooled to room temperature. The solution was then transferred to a serum bottle. Titration of this solution following Waston's procedure[97] gave a concentration of 0.39 M. The solution was stable for a month at room temperature. However, it was found that at a higher concentration than 0.4 M, isopropenylmagnesium bromide crystallized from the solution on standing.

Methyl (1α,2β,4aβ,5α,8aα)-1,2,3,5,8,8a-Hexahydro-8-methylene-2-(1-methyl)ethenyl-4-oxo-1,5,8a-trihydroxy-4a(4H)-naphthalenecarboxylate (122).



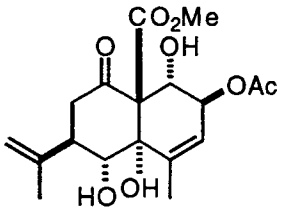
To a stirred solution of isopropenylmagnesium bromide (0.39 M in THF, 0.57 mL, 0.221 mmol) in 0.5 mL of tetrahydrofuran was added solid cuprous bromide dimethylsulfide complex (3 mg, 0.0142 mmol) at -78 °C. After 3 min a yellowish solution resulted and a solution of **98** (13.5 mg, 0.0355 mmol), hexamethylphosporic triamide (74 μL, 0.426 mmol), and trimethylsilyl chloride

(54 μL, 0.426 mmol) in 1 mL of tetrahydrofuran was added dropwise via the wall of the flask through a double-tipped needle. Stirring was continued for 15 min and the mixture was quenched with aqueous ammonium chloride and was extracted with diethyl ether (10 mL). The separated organic layer was dried and concentrated in vacuo to give crude **121**.

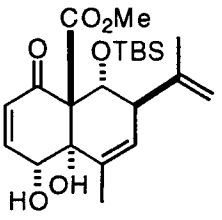
The crude **121** was dissolved in 2 mL of methylene chloride and was treated with excess of triethylamine-hydrofluoric acid complex at room temperature. After 15 h the mixture was passed through a short pad of silica gel with diethyl ether as eluent. and the concentrated eluent was purified by column chromatography (hexane-ethyl acetate, 6:1 to 2:1) to give 2.7 mg (25%) of **122** and 6 mg (50%) of **110**. Spectroscopic data for **122**: IR (film) 3482, 3436, 3397, 1716, 1430, 1236, 1194, 1109, 1077, 1038, 998, 907 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.27 (d, J=10.0 Hz, 1H), 6.14 (s, 1H, OH), 5.90 (dd, J=10.1, 5.4 Hz, 1H), 5.61 (d, J=0.8 Hz, 1H), 5.00 (t, J=1.5 Hz, 1H), 4.97 (s, 1H), 4.87 (dd, J=9.9, 9.5 Hz, 1H), 4.12 (d, J=4.1 Hz, 1H, OH), 3.67 (s, 3H), 2.95 (m, 1H), 2.72 (t, J=14.5 Hz, 1H), 2.40 (dd, J=13.8, 4.4 Hz, 1H), 2.35 (d, J=9.7 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6, 166.6, 143.7, 143.2, 133.6, 123.5, 119.9, 114.4, 78.2, 70.5, 67.5, 66.5, 53.2, 49.4, 42.3, 18.6; MS (CI) *m/z* (rel. intensity) 309 (M + 1, 9), 308 (M, 10), 292 (15), 291 (81), 287 (4), 275 (5), 274 (15), 273 (83), 259 (21), 255 (10), 245 (11), 241 (34), 231 (10), 213 (35), 197 (19), 177 (100); HRMS *m/z* Calcd for $C_{16}H_{21}O_6$ (M + 1): 309.1338. Found: 309.1310.

Enol ether 124. To a stirred solution of isopropenylmagnesium bromide (0.39 M in THF, 0.54 mL, 0.204 mmol) in 0.5 mL of tetrahydrofuran was added solid cuprous bromide dimethyl sulfide complex (4.2 mg, 0.0204 mmol) at -78 °C. After 2~3 min a yellowish solution resulted and a solution of **95** (22.5 mg, 0.0511 mmol), hexamethylphophoric triamide (107 μL, 0.613 mmol), and trimethylsilyl chloride (78 μL, 0.613 mmol) in 0.5 mL of terahydrofuran was added slowly via the wall of flask through a double-tipped needle. After 15 min an additional quantity of isopropenylmagnesium bromide (0.5 M in THF, 100 μL, 0.05 mmol) was added and stirring was continued for 50 min. The mixture was quenched with aqueous ammonium chloride solution and extracted with diethyl ether (10 mL). The separated organic layer was washed with saturated brine, dried and concentrated in vacuo. The resulting crude **123** was dissolved in 1 mL of a solution of acetic acid, tetrahydrofuran, and water (8:8:1) at room temperature and stirred for 5 h. The mixture was concentrated in vacuo and the residue was purified by column chromatography (hexane-ethyl acetate, 4:1 to 3:1) to give 13 mg (46%) of **124** as an oil: IR (film) 3429, 1737, 1244, 1193, 1115, 1083, 1023, 962, 937, 895, 843, 783 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (s, 1H), 5.29 (br. s, 1H), 4.90 (m, 2H), 4.62 (d, J=2.8 Hz, 1H), 4.43 (dd, J=11.0, 7.6 Hz, 1H), 3.60 (s, 3H), 3.04 (dd, J=7.6, 2.7 Hz, 1H), 2.14 (d, J=11.0 Hz, 1H, OH), 2.07 (s, 5H), 1.71 (s, 3H), 0.88 (s, 9H), 0.21 (s, 15H), 0.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 169.7, 146.6, 146.1, 144.7, 121.0, 113.4, 109.4, 73.9, 73.6, 73.3, 70.8, 58.3, 51.8, 51.7, 25.6, 21.9, 21.1, 19.6, 18.0, 0.3, -4.6, -5.5.

Methyl (1α,2β,4aβ,5α,6β,8aα)-1,5,6,8a-Tetrahydro-6-acetoxy-1,5,8a-trihydroxy-8-methyl-2-(1-methyl)ethenyl-4-oxo-4a(4H)-naphthalenecarboxylate (125). To a stirred solution of triethylamine-hydrofluoric acid complex (9.2 mg, 0.0570 mmol) in 0.5 mL of methylene chloride was added a solution of **124** (10 mg, 0.0190 mmol) in 0.5 mL of methylene chloride at room temperature. After 3 d the mixture was passed through a short pad of silica gel with diethyl ether as eluent and the concentrated eluent was purified by column chromatography (hexane-ethyl acetate, 3:1 to 2:1) to give 5.1 mg (55%) of **109** and 1.1 mg of **125** (16%). Spectroscopic data for **125**: IR (film) 3483, 3456, 3431, 1725, 1435, 1373, 1233, 1101, 1042, 1022, 999, 969, 934, 903, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.48 (m, 1H), 5.25 (m, 1H), 4.96 (t, J=1.5 Hz, 1H), 4.92 (s, 1H), 4.79 (m, 1H), 4.63 (m, 1H), 4.03 (d, J=3.8 Hz, 1H), 2.85 (m, 1H), 2.49 (dd, J=13.8, 13.2 Hz, 1H), 2.38 (dd, J=13.8, 5.8 Hz, 1H), 2.15 (dd, J=1.4, 1.0 Hz, 3H), 2.10 (d, J=10.5 Hz, 1H), 2.00 (s, 3H), 1.77 (s, 3H); MS (CI) *m/z* (rel. intensity) 369 (M + 1, 16), 368 (M^+, 4), 352 (10), 351 (53), 346 (7), 345 (30), 333 (6), 329 (8), 310 (18), 307 (100), 292 (11), 291 (58), 273 (46), 259 (20), 241 (16), 231 (11), 213 (22), 195 (17), 177 (26), 167 (20), 151 (16); HRMS *m/z* Calcd for $C_{18}H_{25}O_8$ (M + 1): 369.1549. Found: 369.1548.

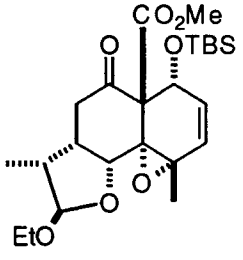


Methyl (1α,4aβ,5α,6β,8aα)-1,5,6,8a-Tetrahydro-5-(*t*-butyldimethylsilyl)oxy-1,8a-dihydroxy-8-methyl-6-(1-methyl)ethenyl-4-oxo-4a(4H)-naphthalenecarboxylate (120). To a stirred solution of isopropenylmagnsium bromide (0.39 M in THF, 365 μL, 0.142 mmol) in 1 mL of tetrahydrofuran was added solid cuprous bromide dimethyl sulfide (6 mg, 0.2 equiv. to the Grignard reagent) at -78 °C. After 3 min a yellowish solution resulted and a solution of **91** (36 mg,



0.0946 mmol) and hexamethylphosphoric triamide (100 μL, 0.568 mmol) in 1 mL of tetrahydrofuran was added dropwise through a double-tipped needle. The resulting mixture was stirred for 1 h at -78 °C and slowly warmed to room temperature during 2 h. The mixture was quenched with aqueous ammonium chloride solution and was extracted with diethyl ether. The separated organic layer was dried and concentrated in vacuo. Column chromatography (hexane-ethyl acetate, 4:1 to 3:1) of the residue afforded 10 mg (25%) of **120** and 24 mg (66%) of recovered **91.** Spectroscopic data for **120**: IR (film) 3543, 3403, 1742, 1700, 1384, 1252, 1219, 1176, 1142, 1090, 1033, 837, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.66 (dd, J=10.3, 2.3 Hz, 1H), 5.93 (dd, J=10.3, 2.1 Hz, 1H), 5.70 (s, 1H, OH), 5.39 (m, 1H), 5.19 (d, J=11.5 Hz, 1H), 5.13 (s, 1H), 4.83 (d, J=1.2 Hz, 1H), 4.55 (s, 1H), 3.37 (s, 3H), 3.25 (d, J=11.5 Hz, 1H, OH), 2.88 (br.s, 1H), 2.12 (t, J=1.5 Hz, 3H), 1.82 (s, 3H), 0.85 (s, 9H), 0.29 (s, 3H), 0.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 166.3, 149.9, 138.2, 125.8, 122.5, 114.2, 75.6, 69.8, 68.9, 64.4, 51.5, 50.6, 25.8, 21.8, 21.3, 17.9, -4.6, -4.9; MS (CI) *m/z* (rel. intensity) 423 (M + 1, 12), 422 (M^+, 2), 408 (6), 407 (23), 406 (27), 405 (100), 389 (14), 365 (23), 347 (11), 301 (6), 291 (10), 273 (50), 259 (4), 241 (14), 207 (12); HRMS *m/z* Calcd for $C_{22}H_{34}O_6Si$ (M^+): 422.2124. Found: 422.2123.

Methyl (1α,4α,5α,6α,11R*,12R*)-1-(*t*-Butyldimethylsilyl)oxy-4,5-epoxy-(7βH)-6,12-epoxy-12-ethoxy-4-oxo-2-eudesmen-14-oate (127b). To a stirred



solution of **91** (272 mg, 0.715 mmol) in 4 mL of propenyl ethyl ether (distilled over sodium) was added N-bromosuccinimide (636 mg, 3.574 mmol) in four portions over 10 min at 0 °C. After 30 min the mixture was passed through a short pad of silica gel (10 g) with hexane-ethyl

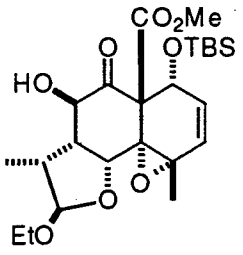
acetate (6:1) as eluent, and the concentrated eluent was purified by column chromatography (hexane-ethyl acetate, 9:1 to 6:1) to give 317 mg (81%) of **126** as a diastereomeric mixture.

A mixture of **126** (317 mg, 0.581 mmol), tri-*n*-butyltin hydride (203 μL, 0.7554 mmol), and 2,2'-azobisisobutyronitrile (AIBN, 6 mg, 0.0378 mmol) in 25 mL of benzene was refluxed for 4 h. The mixture was cooled to room temperature and the volatile material was removed in vacuo. The residue was dissolved in 5 mL of reagent grade diethyl ether and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 124 μL, 0.831 mmol) was added with shaking.[98] After 2~3 min the mixture was passed through a short pad of silica gel with diethyl ether as eluent, and the concentrated eluent was purified by radial chromatography (2 mm, hexane-ethyl acetate, 10:1 to 6:1) to give 36.2 mg of **127a**, 58.7 mg of **127c** , 71.1 mg of **127b** , and 68 mg of a mixture in 86% yield. Spectroscopic data for **127b** ; IR (film) 1747, 1723, 1254, 1214, 1139, 1084, 979, 966, 858, 838, 862, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.01 (d, J=9.7 Hz, 1H), 5.88 (dd, J=9.7, 6.1 Hz, 1H), 4.98 (d, J=7.3 Hz, 1H), 4.93 (d, J=6.1 Hz, 1H), 4.84 (d, J=2.7 Hz, 1H), 3.70 (m, 1H), 3.68 (s, 3H), 3.68 (s, 3H), 3.47 (m, 1H), 2.77 (m, 1H), 2.65 (dd, J=15.7, 13.5 Hz, 1H), 2.38 (m, 2H), 1.70 (s, 3H), 1.20 (t, J=7.0 Hz, 3H), 1.02 (d, J=7.4 Hz, 3H), 0.80 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.5, 167.6, 135.4, 131.11, 109.3, 73.6, 70.0, 67.2, 65.8, 63.5, 63.1, 57.3, 53.0, 41.7, 39.9, 38.6, 25.6, 17.8, 16.9, 15.2, 12.8, -3.8, -5.1; MS (CI) *m/z* (rel. intensity) 467 (M + 1, 25), 465 (9), 452 (10), 451 (32), 450 (10), 449 (29), 435 (15), 423 (11), 422 (30), 421 (100), 409 (21), 405 (27), 390 (10), 389 (34), 363 (28), 335 (17), 289 (18), 253 (30), 213 (18), 143 (16), 133 (20), 59 (77), 57 (88); HRMS *m/z* Calcd for $C_{24}H_{39}O_7Si$ (M + 1): 467.2465. Found: 467.2462.

Spectroscopic data for **127a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 (d, J=9.6 Hz, 1H), 5.89 (dd, J=9.6, 5.9 Hz, 1H), 5.02 (d, J=4.7 Hz, 1H), 4.95 (d, J=8.8 Hz, 1H), 4.90 (d, J=6.0 Hz, 1H), 3.72 (m, 1H), 3.69 (s, 3H), 3.46 (m, 2H), 2.65 (m, 2H), 2.38 (m, 1H), 2.01 (m, 1H), 1.73 (s, 3H), 1.86 (t, J=7.1 Hz, 3H), 1.04 (d, J=6.9 Hz, 3H), 0.80 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H).

Acetal 134. Following the same procedure as used for the conversion of **91** to **127**, **95** (34.2 mg, 0.0776 mmol) produced 38 mg (82%) of the bromoacetal. Cyclization of the bromoacetal yielded 21 mg (55%) of **134** as an inseparable mixture of diastereomers.

Methyl (1α,4α,5α,6α,8β,11R*,12R*)-1-(*t*-Butyldimethylsilyl)oxy-4,5-epoxy-(7βH)-6,12-epoxy-12-ethoxy-8-hydroxy-4-oxo-2-eudesmen-14-oate (129).

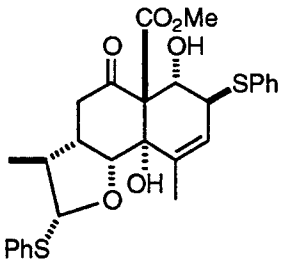


To a stirred solution of sodium hexamethyldisilazide (1 M in THF, 72 μL, 0.072 mmol) in 0.5 mL of tetrahydrofuran was added a solution of **127b** (26 mg, 0.0557 mmol) in 0.5 mL of tetrahydrofuran at -78 °C. After 30 min a solution of *trans*-2-(phenylsulfonyl)-3-phenyloxaziridine (22 mg, 0.084 mmol) in 0.5 mL of tertahydrofuran was added via a double-tipped needle and stirring was continued for 15 min at -78 °C. The mixture was quenched with aqueous ammonium chloride solution and was extracted with diethyl ether (5 mL x 2). The combined organic layer was dried and concentrated in vacuo. Column chromatography (hexane-ethyl acetate, 9:1 to 6:1) of the residue afforded 5.1 mg (19%) of **129** as an oil: IR (film) 3501, 1748, 1727, 1391, 1379, 1252, 1111, 1081, 1008, 969, 851, 839, 778 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (d, J=9.8 Hz, 1H), 5.87 (dd, J=9.8, 6.0 Hz, 1H), 4.96 (d, J=9.8 Hz, 1H), 4.89 (d, J=6.0 Hz, 1H), 4.85 (s, 1H), 4.59 (dd, J=11.7, 4.1 Hz, 1H), 3.73 (s, 3H), 3.67 (m,

1H), 3.43 (m, 1H), 3.30 (d, J=4.1 Hz, 1H, OH), 2.77 (m, 1H), 2.52 (m, 1H), 1.75 (s, 3H), 1.18 (m, 5H), 0.80 (s, 9H), 0.02 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 167.3, 136.2, 130.7, 109.4, 73.8, 72.1, 70.4, 67.3, 62.6, 61.8, 58.9, 53.2, 46.1, 40.5, 25.5, 17.7, 17.1, 15.1, 13.0, -3.8, -5.2; MS (CI) *m/z* (rel. intensity) 483 (M + 1, 33), 467 (40), 465 (23), 438 (28), 437 (100), 425 (29), 405 (26), 389 (21), 363 (25), 351 (66), 277 (20), 253 (27), 213 (74), 133 (22); HRMS *m/z* Calcd for $C_{24}H_{39}O_8Si$ (M + 1): 483.2414. Found: 483.2414.

The separated aqueous layer was acidified to pH 1 by addition of 2 N hydrochloric acid solution and was extracted with diethyl ether (10 mL X 2). The combined organic layer was dried and concentrated in vacuo, and the residue was passed through a short pad of silica gel with ethyl acetate as eluent. The concentrated eluent was dissolved in diethyl ether (1 mL) and treated with excess diazomethane at room temperature, then concentrated in vacuo. Thin layer chromatography (0.25 mm, hexane-ethyl acetate, 3:1) of the residue afforded 5 mg (24%) of **130** as a yellowish oil: IR (film) 1738, 1717, 1437, 1257, 1215, 1161, 1104, 1056, 986 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.30 (d, J=11.0 Hz, 1H), 6.11 (dd, J=11.0, 5.4 Hz, 1H), 5.48 (d, J=9.3 Hz, 1H), 5.46 (d, J=5.4 Hz, 1H), 4.79 (s, 1H), 3.74 (s, 3H), 3.69 (m, 1H), 3.63 (s, 3H), 3.42 (m, 1H), 3.38 (m, 1H), 2.41 (m, 3H), 2.01 (s, 3H), 1.78 (t, J=7.1 Hz, 3H), 1.00 (d, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 166.9, 159.8, 156.7, 129.7, 126.6, 122.4, 113.1, 110.0, 76.3, 62.8, 52.2, 51.5, 41.8, 39.7, 31.2, 20.0, 15.2, 12.2.

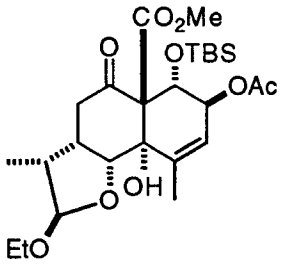
Methyl (1α,2β,5α,6α,11S*,12R*)-1,5-Dihydroxy-(7βH)-6,12-epoxy-2,12-diphenylthio-4-oxo-2-eudesmen-14-oate (132). To a stirred solution of **127a**



(8.4 mg, 0.0180 mmol) and thiophenol (7.9 μL, 0.072 mmol) in 0.5 mL of methylene chloride was added neat boron trifluoride etherate (8.8 μL, 0.072 mmol) at 0 °C. After 30 min the mixture was neutralized with a few drops of triethylamine and was passed through a short pad of silica gel with methylene chloride as eluent. Column chromatography (hexane-ethyl acetate, 6:1 to 3:1) of the concentrated eluent afforded 4 mg (42%) of **132** as a colorless solid: IR (film) 3452, 3440, 1722, 1438, 1231, 1207, 1185, 1090, 1016, 999, 975, 912, 739, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.5~7.2 (m, 10H), 5.61 (m, 1H), 5.21 (d, J=5.1 Hz, 1H), 5.06 (d, J=7.1 Hz, 1H), 4.90 (d, J=8.1 Hz, 1H), 4.35 (s, 1H, OH), 4.12 (d, J=7.1 Hz, 1H, OH), 3.74 (s, 3H), 2.82 (dd, J=18.1, 11.1 Hz, 1H), 2.65 (dd, J=18.1, 6.6 Hz, 1H), 2.22 (m, 2H), 2.00 (t, J=1.5 HZ, 3H), 1.24 (d, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 166.5, 139.3, 135.3, 134.8, 129.3, 129.2, 127.4, 127.1, 120.6, 94.2, 80.2, 72.8, 71.5, 64.5, 52.9, 49.6, 46.7, 42.3, 40.8, 19.7, 18.5; MS (CI) *m/z* (rel. intensity) 527 (M + 1, 0.25), 509 (M - OH, 2), 461 (3), 433 (3), 399 (23), 351 (12), 323 (75), 307 (29), 215 (16), 139 (31), 111 (100); HRMS *m/z* Calcd for $C_{28}H_{29}O_5S_2$ (M - OH): 509.1456. Found: 509.1436.

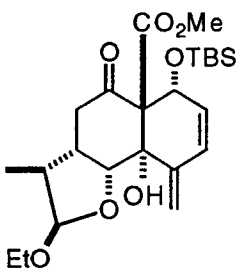
Compound **132** crystallized from octane in the space group P-1 with a=8.354 (2) Å, b=12.569 (3) Å, c=112.934 (2) Å, α=91.33 (3)°, β=93.77 (2)°, γ=94.11 (3)°, z=2 and d_{calcd}=1.363 g/cm^3. The intensity data were measured on a Siemens P4 diffractometer (Cu Kα radiation). There were 3328 unique reflections and the structure was solved by direct methods. The final discrepancy indices were R=0.0688 and Rw=0.0672.

Methyl (1α,2α,5α,6α,11R*,12R*)-2-Acetoxy-1-(*t*-butyldimethylsilyl)oxy-5-hydroxy-(7βH)-6,12-epoxy-12-ethoxy-4-oxo-3-eudesmen-14-oate (131). A



solution of **127b** (36.2 mg, 0.0776 mmol) in 1 mL of acetic acid was stirred overnight (20 h) at room temperature and then was heated to 70 °C for 1 h and concentrated in vacuo. Radial chromatography (1 mm, hexane-ethyl acetate, 9:1 to 6:1) of the residue afforded 10 mg (25%) of **131** and 13 mg of an unidentified side product. Spectroscopic data for **131**: IR (film) 3436, 1731, 1234, 1077, 1021, 973, 839 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.45 (m, 1H), 5.22 (m, 2H), 4.88 (m, 3H), 3.76 (m, 1H), 3.62 (s, 3H), 3.48 (m, 1H), 2.63 (d, J=10.0 Hz, 2H), 2.10 (s, 3H), 2.05~1.8 (2H), 1.97 (s, 3H), 1.20 (t, J=7.3 Hz, 3H), 1.05 (d, J=7.3 Hz, 3H), 0.79 (s, 9H), 0.27 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 169.6, 165.6, 145.3, 116.7, 104.1, 75.7, 72.8, 72.1, 69.5, 64.5, 62.7, 52.8, 46.8, 42.9, 39.7, 25.7, 20.9, 20.3, 17.8, 15.1, 12.8, -4.9, -5.5; MS (CI) *m/z* (rel. intensity) 527 (M - OH, 14), 497 (18), 493 (24), 467 (19), 465 (15), 452 (18), 421 (64), 437 (48), 423 (62), 421 (30), 419 (23), 407 (23), 405 (50), 305 (100), 287 (50), 259 (35); HRMS *m/z* Calcd for $C_{26}H_{41}O_8Si$ (M - OH): 509.2571. Found: 509.2346.

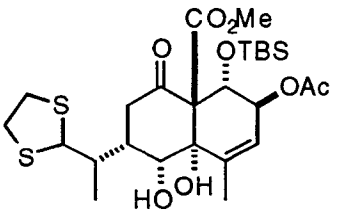
Methyl (1α,5α,6α,11R*,12R*)-1-(*t*-Butyldimethylsilyl)oxy-5-hydroxy-(7βH)-6,12-epoxy-12-ethoxy-4-oxo-2,4(15)-eudesmadien-14-oate (133). To a



stirred solution of **127a** (22.5 mg, 0.0482 mmol) in 2 mL of methylene chloride was added neat boron trifluoride diethyl etherate (18 μL, 0.145 mmol) at -40 °C. After 20 min the mixture was warmed to -10 °C over 20 min and was quenched with a few drops of triethylamine. The resulting

mixture was passed through a short pad of silica gel with hexane -ethyl acetate (3:1) as eluent and the concentrated eluent was purified by thin layer chromatography (0.25 mm, hexane-ethyl acetate, 3:1) to give 6 mg (27%) of **133**: IR (film) 3425, 1746, 1719, 1248, 1215, 1156, 1107, 1075, 1037, 1016, 987, 916, 842, 782 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.22 9d, J=10.0 Hz, 1H), 5.91 (dd, J=10.0, 5.6 Hz, 1H), 5.75 (s, 1H), 5.49 (d, J=1.1 Hz, 1H), 5.19 (s, 1H), 5.11 (d, J=4.4 Hz, 1H), 5.00 (d, J=5.3 Hz, 1H), 4.81 (dd, J=9.8, 1.0 Hz, 1H), 3.78 (m, 1H), 3.59 (s, 3H), 3.54 (m, 1H), 2.79 (m, 2H), 2.47 (m, 1H), 2.05 (m, 1H), 1.21 (t, J=7.1 Hz, 3H), 1.05 (d, J=7.1 Hz, 3H), 0.79 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6, 167.6, 143.1, 130.6, 126.4, 117.6, 104.9, 76.7, 74.7, 69.6, 63.7, 62.8, 52.8, 47.5, 44.3, 40.3, 25.5, 17.7, 15.2, 12.1, -4.4, -5.5; MS (CI) *m/z* (rel. intensity) 467 (M + 1, 5), 449 (45), 433 (10), 421 (39), 405 (30), 375 (10), 363 (33), 335 (100), 317 (59), 289 (83), 177 (20); HRMS *m/z* Calcd for $C_{24}H_{39}O_7Si$ (M + 1): 467.2465. Found: 467.2465.

Dithioacetal 136. To a stirred solution of **134** (8 mg, 0.0157 mmol) and ethanedithiol (6 μL, 0.0626 mmol) in 0.5 mL of methylene chloride was added boron trifluoride etherate (7.7 μL, 0.0626 mmol) at 0 °C. After 5 min the mixture was quenched with saturated aqueous ammonium chloride solution and was extracted with diethyl ether (2 X 5 mL). The combined organic layer was washed with saturated brine, dried and concentrated, and the residue was purified by column chromatography (hexane-ethyl acetate, 3:1 to 1:1) to give 3.5 mg (49%) of **136** as a single diastereomer: IR (film) 3481, 3438, 3428, 3403, 1735, 1432, 1405, 1371, 1233, 1181, 1157, 1057, 1017, 973, 936, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.54 (m, 1H), 5.26 (d, J=5.0 Hz, 1H), 5.12 (d, J=4.0 Hz, 1H), 4.76 (d,

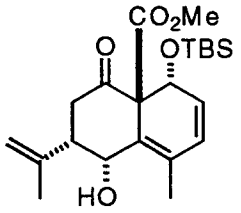


J=4.3 Hz, 1H), 4.46 (s, 1H, OH), 4.43 (dd, J=5.2, 9.9 Hz, 1H), 3.74 (s, 3H), 3.56 (d, J=4.6 Hz, 1H, OH), 3.44 (d, J=9.9 Hz, 1H, OH), 3.20 (s, 4H), 2.50 (m, 2H), 2.27 (m, 1H), 2.05 s, 3H), 1.98 (s, 3H), 1.06 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 169.3, 166.4, 143.4, 118.4, 71.9, 70.8, 68.5, 68.4, 64.2, 57.2, 53.0, 39.6, 39.1, 38.9, 38.6, 37.0, 20.9, 19.2, 13.1; MS (CI) *m/z* (rel. intensity) 461 (M + 1, 4), 445 (11), 444 (17), 443 (71), 425 (38), 401 (38), 384 (23), 383 (100), 365 (33), 359 (55), 351 (32), 307 (30), 289 (20), 233 (15), 217 (44), 167 (44), 157 (23); HRMS *m/z* Calcd for $C_{20}H_{29}O_8S_2$ (M + 1): 461.1304. Found: 462.1303.

Methyl (1α,4aβ,5α,8α,8aα)-1,5-Dihydro-5-(*t*-butyldimethylsilyl)oxy-1-(2-bromoethenyl)carbonyloxy-8(β)-methyl-4-oxo-4a(4H)-8,8a-epoxynaphthalene-carboxylate (141). To a stirred solution of **91** (38 mg, 0.0999 mmol), triethylamine (42 μL, 0.300 mmol), and a catalytic amount of N,N-dimethylaminopyridine in 0.5 mL of methylene chloride was added 2,3-dibromopropionyl chloride (17.2 μL, 0.150 mmol) at 0 °C. After 2.5 h at 0 °C aqueous sodium bicarbonate solution was added and the mixture was extracted with diethyl ether (8 mL). The separated organic layer was washed with brine, dried and concentrated in vacuo. Column chromatography (hexane-ethyl acetate, 9:1) of the residue afforded 32.5 mg (64%) of **141** and 3.5 mg (10%) of recovered **91.** Spectroscopic data for **141**: IR (film) 1731, 1693, 1253, 1209, 1097, 1035, 857, 839, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J=2.2 Hz, 1H), 6.77 (dd, J=10.3, 1.8 Hz, 1H), 6.55 (t, J=2.2 Hz, 1H), 6.41 (d, J=2.0 HZ, 1H), 6.21 (dd, J=10.3, 2.6 Hz, 1H), 5.95 (m, 2H), 5.10 (dd, J=3.8, 2.8 Hz, 1H), 3.69 (s, 3H), 1.58 (s, 3H), 0.80 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 166.9, 160.7, 146.9, 135.2,

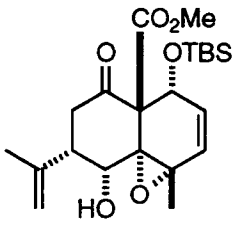
132.7, 131.8, 129.4, 120.7, 68.1, 67.7, 66.8, 63.9, 57.1, 53.4, 25.7, 17.9, 17.5, -4.0, -5.0.

Methyl (1α,2α,4aβ,5α)-1,2,3,5-Tetrahydro-5-(*t*-butyldimethylsilyl)oxy-1-hydroxy-8-methyl-2-(1-methyl)ethenyl-4-oxo-4a(4H)-naphthalenecarboxylate (147). To a stirred solution of diisopropylamine (13 μL, 0.0921 mmol) was added dropwise *n*-butyllithium (1.6 M in hexane, 58 μL, 0.0921 mmol) at 0 °C. After 30 min **94** (35 mg, 0.0960 mmol) was added portionwise to the resulting lithium diisopropylamide solution at -78 °C. After 5 min neat 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU, 110 μL, 0.920 mmol) was added dropwise and stirring was continued for 15 min. To the mixture was added dropwise a solution of isopropenylmagnesium bromide (460 μL, 0.4 M in THF) and stirring was continued for 21 h at -78 °C. The mixture was quenched with aqueous ammonium chloride solution and was extracted with diethyl ether (6 mL X 2). The combined organic layer was washed with saturated brine, dried and concentrated. Column chromatography (hexane-ethyl acetate, 6:1 to 3:1) of the residue afforded 8 mg (21%) of **147** and 8.6 mg (25%) of recovered **94**. Spectroscopic data for **147**: IR (film) 3548, 3508, 1743, 1716, 1251, 1225, 1073, 1049, 841, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.97 (dd, J=9.4, 5.1 Hz, 1H), 5.88 (d, J=9.4 Hz, 1H), 5.05 (s, 1H), 4.96 (s, 1H), 4.89 (d, J=5.3 Hz, 1H), 4.81 (s, 1H), 3.63 (s, 3H), 2.93 (br. d, J=14.0 Hz, 1H), 2.75 (dd, J=16.0, 13.0 Hz, 1H), 2.45 (m, 1H), 2.01 (s, 3H), 1.91 (s, 3H), 1.40 (d, J=2.9 Hz, 1H, OH), 0.78 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 168.3, 143.8, 133.3, 131.3, 128.9, 127.7, 112.8, 67.3, 64.6, 52.9, 42.0, 39.1, 25.5, 22.2, 18.0, 17.8, -4.2, -5.2; MS (CI) *m/z* (rel. intensity) 407 (M + 1, 11), 391 (20), 390 (12), 389 (46), 373 (19), 371 (19), 349



(27), 341 (26), 331 (21), 299 (23), 275 (100), 271 (17), 257 (91), 243 (62); HRMS Calcd for $C_{22}H_{35}O_5Si$ (M + 1): 407.2253. Found: 407.2252.

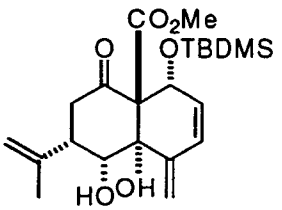
Methyl (1α,2α,4aβ,5α,8α,8aα)-1,2,3,5,8,8a-Hexahydro-5-(*t*-butyldimethylsilyl)oxy-1-hydroxy-8(β)-methyl-2-(1-methyl)ethenyl-4-oxo-4a(4H)-8,8a-epoxynaphthalenecarboxylate (145). To a stirred solution of



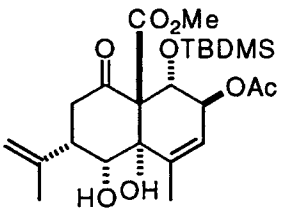
diisopropylamine (1.89 mL, 0.0921 mmol) in 30 mL of tetrahydrofuran was added *n*-butyllithium (1.6 M in hexane, 1.89 mL, 13.46 mmol) dropwise at 0 °C. After 30 min the resulting lithium diisopropylamide solution was added to a stirred solution of **91** (4.88 g, 12.82 mmol) in 30 mL of tetrahydrofuran which was cooled to -78 ° C and the mixture was stirred for 15 min. A solution of 15-crown-5 (3.05 mL, 15.38 mmol) in 10 mL of tetrahydrofuran was added and stirring was continued for 15 min. To the mixture was added isopropylmagnesium bromide (0.39 M in THF, 34.4 mL, 15.38 mmol) and stirring was continued for 30 min at -78 °C. The mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was quenched with aqueous ammonium chloride solution and was extracted with diethyl ether (50 mL X 2). The combined organic layer was washed with brine, dried and concentrated in vacuo. Column chromatography (hexane-ethyl acetate, 4:1)of the residue afforded 3.23 g (60%) of **145** and 1.24 g (25%) of recovered **91**. Spectroscopic data for **145**: IR (film) 3479, 1752, 1723, 1251, 1203, 1096, 841, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.02 (d, J=9.6 Hz, 1H), 5.91 (dd, J=9.6, 6.3 Hz, 1H), 5.02 (d, J=6.1 Hz, 1H), 5.00 (d, J=0.9 Hz, 1H), 4.72 (s, 1H), 4.51 (ddd, J=4.3, 4.3, 1.7 Hz, 1H), 3.69 (s, 3H), 2.93 (d, J=4.4 Hz, 1H, OH), 2.69 (d, J=14.9 Hz, 1H), 2.53 (m, 2H), 1.90 (s, 3H), 1.63 (s, 3H), 0.81 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 167.3, 143.2, 133.9,

131.4, 112.1, 69.1, 67.1, 63.89, 63.80, 58.3, 53.3, 42.9, 39.9, 25.5, 21.9, 17.7, 16.6, -4.0, -5.1; MS (CI) *m/z* (rel. intensity) 423 (M+1, 66), 407 (48), 406 (25), 405 (83), 391 (20), 389 (22), 373 (26), 291 (51), 277 (32), 273 (31), 259 (32), 249 (23), 241 (25), 231 (22), 213 (31), 177 (39), 165 (24), 59 (100); HRMS Calcd for $C_{22}H_{35}O_6Si$ (M + 1): 423.2203. Found: 423.2202.

Methyl (1α,2α,4aβ,5α,8aα)-1,2,3,5,8,8a-Hexahydro-5-(*t*-butyldimethylsilyl)-oxy-1,8a-dihydroxy-8-methylene-2-(1-methyl)ethenyl-4-oxo-4a(4H)-naphthalenecarboxylate (148). To a stirred solution of **145** (4.3 mg, 0.0108 mmol) in 0.5 mL of toluene was added neat titanium tetraisopropoxide (12 μL, 0.0407 mmol) at room temperature. After 18 h the mixture was passed through a short pad of silica gel with methylene chloride as eluent to give 3.7 mg (86%) of **148**: IR (film) 3535, 3356, 1724, 1404, 1241, 1184, 1149, 1108, 1076, 1036, 1011, 884, 844, 785 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.40 (s, 1H, OH), 6.28 (d, J=9.8 Hz, 1H), 5.97 (s, 1H), 5.84 (dd, J=9.7, 5.7 Hz, 1H), 5.32 (s, 1H), 5.22 (d, J=5.6 Hz, 1H), 4.97 (s, 1H), 4.90 (dd, J=10.4, 6.0 Hz, 1H), 4.66 (s, 1H), 3.64 (s, 3H), 3.54 (d, J=10.4 Hz, 1H, OH), 3.03 (t, J=15.5 Hz, 1H), 2.73 (m, 1H), 2.43 (d, J=16.0, 1.7 Hz, 1H), 1.92 (s, 3H), 0.84 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 166.3, 145.6, 144.0, 133.0, 124.2, 118.4, 111.2, 73.6, 69.7, 68.9, 65.7, 53.1, 42.1, 39.1, 25.5, 22.5, 17.7, -4.5, -5.5; LRMS (CI) *m/z* (relative intensity) 423 (M + 1, 5), 407 (13), 389 (5), 365 (14), 347 (6), 319 (5), 301 (40), 291 (26), 273 (18), 259 (10), 241 (33), 227 (14), 213 (20), 177 (100), 133 (12); HRMS *m/z* Calcd for $C_{22}H_{35}O_6Si$ (M + 1): 423.2203. Found: 423.2202.



Methyl (1α,2α,4aβ,5α,6β,8aα)-1,5,6,8a-Tetrahydro-6-acetoxy-5-(*t*-butyldimethylsilyl)oxy-1,8a-dihydroxy-8-methyl-2-(1-methylethenyl)-4-oxo-4a(4H)-naphthalenecarboxylate (149). A solution of **145** (5.2 mg, 0.0123 mmol) in



0.5 mL of acetic acid was heated at 60 - 65 °C for 4h. All of the volatile material was evaporated in vacuo and the residue was purified by column chromatography (hexane-ethyl acetate, 4:1 to 3:1) to give 4.0 mg (67%) of **149** and 1.5 mg (19%) of **148**. Spectroscopic data for **149**: IR (film) 3535, 3384, 1735, 1438, 1370, 1231, 1153, 1104, 1071, 1020, 838, 785 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.43 (m, 1H), 5.31 (s, 1H), 5.12 (d, J=5.0 Hz, 1H), 4.93 (s, 1H), 4.85 (d, J=1.4 Hz, 1H), 4.61 (s, 1H), 4.56 (m, 1H), 3.68 (s, 3H), 3.33 (br. d, J=10.4 Hz, 1H), 2.87 (dd, J=17.5, 15.0 Hz, 1H), 2.50 (m, 2H), 2.08 (s, 3H), 1.98 (s, 3H), 1.86 (s , 3H), 0.82 (s, 9H), 0.28 (s, 3H), 0.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 169.6, 166.6, 144.9, 143.7, 117.1, 111.4, 72.3, 72.0, 69.2, 68.0, 64.5, 52.7, 41.7, 38.3, 25.7, 22.3, 20.9, 19.4, 17.8, -4.9, -5.5; LRMS (CI) *m/z* (relative intensity) 483 (M + 1, 12), 467 (10), 466 (22), 465 (65), 449 (24), 433 (10), 425 (11), 424 (22), 423 (72), 409 (17), 408 (10), 407 (41), 406 (17), 405 (58), 391 (17), 389 (22), 381 (16), 373 (10), 366 (12), 365 (49), 351 (33), 349 (12), 347 (23), 335 (11), 333 (39), 323 (29), 301 (13), 291 (22), 273 (100), 267 (12), 259 (12), 249 (77), 219 (44), 177 (33); HRMS *m/z* Calcd for $C_{22}H_{35}O_6Si$ (M + 1): 423.2203. Found: 423.2202.

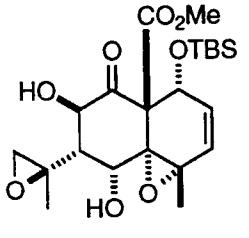
Methyl (1α,2β,6α,11R*)-2-Acetoxy-1-(*t*-butyldimethylsilyl)oxy-6-hydroxy-13-iodo-9-oxo-(7βH)-5,11-epoxy-8-eudesmen-14-oate (150a). To a stirred solution of **149** (37 mg, 0.766 mmol) and solid sodium bicarbonate (64 mg, 0.766 mmol) in 1 mL of acetonitrile in an amber colored bottle was added iodine (49 mg, 0.192 mmol) at room temperature. After 10 h, the mixture was treated with aqueous sodium bisulfite solution and was extracted with diethyl ether (10 mL). The separated organic layer was washed with saturated brine, dried and concentrated in vacuo. Column chromatography (hexane-ethyl acetate, 3:1) of the residue afforded 30 mg (64%) of **150** as a 4:1 diastereomeric mixture based on ^{1}H NMR analysis: MS (CI) *m/z* (rel. intensity) 609 (M + 1, 16), 550 (14), 549 (49), 533 (25), 531 (16), 491 (34), 482 (22), 481 (68), 465 (13), 424 (23), 422 (47), 421 (100), 407 (34), 405 (64), 403 (28), 389 (42), 365 (40), 363 (22), 349 (22), 333 (22), 309 (27), 307 (22), 291 (61), 289 (38), 277 (38), 177 (52); HRMS *m/z* Calcd. for $C_{24}H_{38}IO_8Si$ (M + 1): 609.1381. Found: 609.1383.

Methyl (1α,2β,6α,11R*)-2-Acetoxy-1-(*t*-butyldimethylsilyl)oxy-(7βH)-5,11-epoxy-6-hydroxy-8,11-methano-9-oxo-8-eudesmen-14-oate (151). To a stirred solution of **150** (15 mg, 0.0247 mmol) and 18-crown-6 (7.8 mg, 0.0296 mmol) in 0.2 mL of toluene was added solid cesium acetate (19 mg, 0.0986 mmol) at room temperature. After the addition was complete, the mixture was heated at 60 - 65 °C for 90 h. The mixture was quenched with aqueous sodium bicarbonate and was extracted with diethyl ether (10 mL). The separated organic layer was dried and concentrated in vacuo, and the residue was purified by column chromatography (hexane-ethyl acetate, 5:1 to 2:1) to give

5.5 mg (47%) of **151** as a colorless solid: mp 154 - 155 °C; IR (film) 3537, 1737, 1229, 1114, 1087, 1010, 980, 947, 840, 780, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.60 (m, 1H), 5.51 (t, J=1.7 Hz, 1H), 5.11 (s, 1H), 5.10 (d, J=4.3 Hz, 1H), 3.69 (s, 3H), 3.00 (m, 3H), 2.28 (dd, J=11.8, 9.5 Hz, 1H), 2.11 (s, 3H), 1.97 (t, J=1.9 Hz, 3H), 1.47 (s, 3H), 0.83 (s, 9H), 0.14 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.4, 170.5, 168.9, 137.3, 130.1, 89.0, 85.3, 77.4, 75.0, 74.3, 71.3, 52.9, 50.7, 45.2, 35.3, 25.9, 25.5, 21.3, 20.7, 18.2, -4.4, -5.3; MS (CI) *m/z* (rel. intensity) 527 (M + 1, 33), 463 (11), 423 (15), 422 (30), 421 (100), 406 (30), 405 (54), 403 (30), 390 (23), 389 (72), 373 (29), 371 (58), 363 (61), 331 (19), 289 (28), 261 (47), 229 (27); HRMS, *m/z* Calcd. for $C_{24}H_{37}O_8Si$ (M + 1): 481.2258. Found: 481.2257; Anal. Calcd for $C_{24}H_{36}O_8Si$: C, 59.97; H, 7.56. Found: C, 59.66; H, 7.66.

Compound **151** crystallized from octane in the space group P2(1)/c with a=11.151 (2) Å, b=12.740 (3) Å, c=19.203 (4) Å, β=103.39 (3)°, z=4 and d_{calcd}=1.203 g/cm^3. The intensity data were measured on a Siemens P4 diffractometer (Cu Kα radiation). There were 3071 unique reflections and the structure was solved by direct methods. The final discrepancy indices were R=0.0608 and Rw=0.0596.

Methyl (1α,2α,3β,4aβ,5α,8α,8aα)-1,2,3,5,8,8a-Hexahydro-5-(*t*-butyldimethylsilyl)oxy-1,3-dihydroxy-8(β)-methyl-2-[1(S*)-methyl]epoxyethenyl-4-oxo-4a(4H)-8,8a-epoxynaphthalenecarboxylate (157). Trimethylsilyl chloride (1.27 mL, 10.0 mmol, freshly distilled from CaH_2) was dissolved in tetrahydrofuran (5 mL) in a dry 15 mL centrifuge tube fitted with a rubber septum. Triethylamine (0.1 mL) was added and the solution was diluted to the 10 mL mark with tetrahydrofuran. After 10 min the



mixture was centrifuged and the supernatant used immediately.[99]

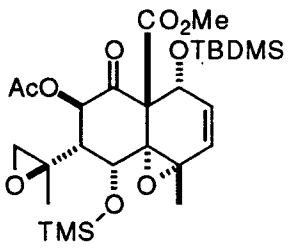
To a stirred solution of diisopropylamine (75 μL, 0.537 mmol) in 0.5 mL of tetrahydrofuran was added *n*-butyllithium (1.6 M in hexane, 335 μL, 0.537 mmol) dropwise at 0 °C. After 30 min the resulting lithium diisopropylamide solution was cooled to -78 °C and the stock solution of trimethylsilyl chloride (1 M in THF, 1.28 mL, 1.278 mmol) was added dropwise via the wall of the flask. Immediately after the addition of trimethylsilyl chloride, a solution of **145** (108 mg, 0.226 mmol) in 2 mL of tetrahydrofuran was added dropwise. Since the reactant was not completely comsumed after 1 h, additional lithium diisopropylamide (1.5 M in cyclohexane, 100 μL, 0.15 mmol) was added dropwise via the wall of the flask and stirring was continued for 20 min. The mixture was quenched with aqueous sodium bicarbonate solution and was warmed to room temperature and extracted with diethyl ether (15 mL). The separated organic layer was washed with saturated brine, dried and concentrated in vacuo to give 121 mg of **155**.

To a stirred solution of **155** (121 mg, 0.209 mmol) in 4 mL of hexane was added *m*-chloroperbenzoic acid (100 mg, 0.48 mmol) at 0 °C. After the addition was complete the mixture was warmed to room temperature and stirring was continued for 19 h. The mixture was diluted with hexane (10 mL) and saturated sodium bicarbonate and was stirred vigorously for 10 min. The organic layer was separated, washed with brine, dried , and concentrated in vacuo. The resulting crude product was dissolved in 1.5 mL of methylene chloride and treated with triethylamine-hydrofluoric acid complex (200 mg, 1.65 mmol). Stirring was continued for 10 h at room temperature. The mixture was passed through a short pad of silica gel with diethyl ether as eluent, and the concentrated eluent was purified by column chromatography (hexane-ethyl acetate, 9:1 to 2:1) to give 21 mg (23%) of **157** and 43 mg (40%) of **156**.

Spectroscopic data for **157**: IR (film) 3531, 1754, 1725, 1390, 1252, 1112, 1085, 1010, 884, 810, 776, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.01 (d, J=9.6 Hz, 1H), 5.91 (dd, J=9.6, 6.0 Hz, 1H), 5.04 (d, J=6.0 Hz, 1H), 4.65 (t, J=5.2 Hz), 4.42 (dd, J=13.9, 2.7 Hz, 1H), 3.85 (d, J=2.7 Hz, 1H, OH), 3.68 (s, 3H), 2.97 (d, J=5.3 Hz, 1H, OH), 2.74 (m, 2H), 1.79 (dd, J=13.9, 5.1 Hz, 1H), 1.65 (s, 3H), 1.63 (s, 3H), 0.80 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 166.4, 134.2, 131.4, 73.0, 69.6, 65.8, 64.3, 62.8, 58.6, 57.9, 56.4, 53.6, 47.9, 25.5, 20.7, 17.7, 16.3, -4.0, -5.1; MS (CI) *m/z* (rel. intensity) 455 (M + 1, 8), 439 (16), 437 (40), 421 (21), 419 (32), 405 (30), 397 (15), 391 (17), 389 (17), 387 (23), 379 (21), 361 (22), 347 (23), 343 (22), 333 (23), 323 (34), 305 (81), 303 (26), 291 (24), 287 (40), 277 (100), 273 (62), 259 (32), 245 (59), 231 (28), 229 (55), 227 (25), 213 (39), 209 (29), 201 (39), 177 (38), 167 (52); HRMS *m/z* Calcd for $C_{22}H_{39}O_8Si$ (M + 1): 455.2101. Found: 455.2103.

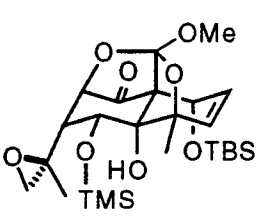
Spectroscopic data for **156**: IR (film) 3501, 1750, 1726, 1219, 1150, 1099, 956, 937, 897 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (d, J=9.6 Hz, 1H), 5.80 (dd, J=9.6, 6.1 Hz, 1H), 4.97 (d, J=9.6 Hz, 1H), 4.86 (d, J=6.1 Hz, 1H), 4.80 (dd, J=9.6, 4.3 Hz, 1H), 3.74 (s, 3H), 3.30 (d, J=4.3 Hz, 1H, OH), 2.79 (d, J=5.0 Hz, 1H), 2.55 (d, J=5.0 Hz, 1H), 1.7~1.8 (1H), 1.81 (s, 3H), 1.56 (s, 3H), 0.83 (s, 9H), 0.19 (s, 9H), 0.03 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 167.3, 137.5, 130.2, 74.7, 70.9, 69.7, 67.4, 63.6, 59.3, 55.9, 55.6, 53.1, 52.4, 25.5, 20.5, 18.7, 17.7, -0.2, -4.2, -5.2; MS (CI) *m/z* (rel. intensity) 527 (M + 1, 9), 511 (22), 495 (10), 493 (11), 479 (11), 451 (11), 437 (41), 419 (66), 405 (22), 395 (30), 391 (19), 379 (31), 363 (30), 345 (22), 331 (20), 313 (22), 305 (45), 295 (23), 281 (31), 277 (38), 245 (28), 243 (21), 212 (59), 133 (43), 75 (100); HRMS *m/z* Calcd for $C_{25}H_{43}O_8Si_2$ (M + 1): 527.2496. Found: 527.2496.

Methyl (1α,2α,3β,4aβ,5α,8α,8aα)-1,2,3,5,8,8a-Hexahydro-3-acetoxy-5-(*t*-butyldimethylsilyl)oxy-1-trimethylsilyloxy-8(β)-methyl-2-[1(S*)-methyl]epoxyethenyl-4-oxo-4a(4H)-8,8a-epoxynaphthalenecarboxylate (160). A mixture



of **156** (31 mg, 0.0589 mmol), acetic anhydride (160 μL, 0.15 mmol) in pyridine (200 μL, 2.5 mmol) was stirred for 16 h at room temperature. The mixture was diluted with diethyl ether (10 mL) and poured into cold aqueous 1N sulfuric acid solution with vigorous stirring. The organic layer was separated, washed with saturated sodium bicarbonate solution, dried, and concentrated in vacuo to give 31 mg (92%) of **160**: IR (film) 1758, 1727, 1252, 1227, 1152, 1120, 1087, 1010, 961, 900, 843, 783, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.97 (d, J=9.7 Hz, 1H), 5.82 (m, 2H), 5.08 (d, J=9.1 Hz, 1H), 4.89 (d, J=6.1 Hz, 1H), 3.71 (s, 3H), 2.55 (d, J=5.0 Hz, 1H), 2.42 (d, J=5.0 Hz, 1H), 2.13 (s, 3H), 2.1~2.2 (1H), 1.55 (s, 3H), 0.85 (s, 9H), 0.19 (s, 9H), 0.05 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 168.6, 167.5, 137.1, 131.0, 75.2, 71.0, 69.1, 67.7, 64.4, 59.5, 55.3, 53.1, 52.6, 51.7, 25.8, 20.9, 20.5, 18.8, 18.2, -0.1, -4.4, -4.6; MS (CI) *m/z* (rel. intensity) 569 (M + 1, 26), 554 (24), 553 (63), 537 (14), 511(45), 509 (18), 493 (30), 479 (54), 477 (26), 461 (26), 447 (27), 437 (31), 435 (26), 419 (100), 405 (34), 403 (31), 377 (36), 295 (47), 213 (75); HRMS *m/z* Calcd for $C_{27}H_{45}O_9Si_2$ (M + 1): 569.2602. Found: 569.2600.

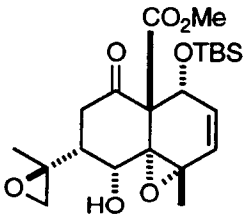
Orthoester 158. A solution of **156** (7 mg, 0.0133 mmol) in 0.5 mL of acetic acid



was heated at 60 - 65 °C for 9 h. The volatile material was removed in vacuo and the residue was purified by column chromatography (hexane-ethyl acetate, 10:1 to 3:1) to give 0.7 mg (10%) of **158**: IR (film) 3431, 1777, 1254, 1229,

1201, 1159, 1130, 1064, 1041, 1023, 908, 842, 781 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.97 (dd, J=9.6, 4.1 Hz, 1H), 5.73 (d, J=9.6 Hz, 1H), 5.44 (s, 1H), 4.66 (d, J=4.3 Hz, 1H), 4.23 (d, J=2.3 Hz, 1H), 3.74 (s, 1H), 3.32 (s, 1H), 2.90 (m, 1H), 2.63 (m, 2H), 1.42 (s, 3H), 1.40 (s, 3H), 0.93 (s, 9H), 0.25 (s, 3H), 0.20 (s, 3H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 133.6, 131.6, 121.6, 87.1, 83.6, 75.3, 68.1, 67.2, 55.6, 55.1, 53.8, 51.5, 50.0, 25.8, 20.9, 18.3, 17.0, 0.9, -4.5, -5.3; MS (CI) *m/z* (rel. intensity) 527 (M + 1, 14), 511 (12), 509 (14), 495 (24), 437 (20), 435 (11), 419 (22), 396 (18), 395 (69), 379 (38), 377 (32), 363 (15), 347 (18), 319 (100), 305 (37), 303 (47), 301 (58), 291 (34), 273 (43), 229 (74), 213 (31), 201 (49), 193 (84), 173 (27); HRMS *m/z* Calcd for $C_{25}H_{43}O_8Si_2$ (M + 1): 527.2496. Found: 527.2496.

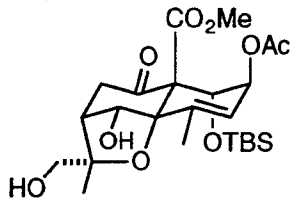
Methyl (1α,2α,4aβ,5α,8α,8aα)-1,2,3,5,8,8a-Hexahydro-5-(*t*-butyldimethylsilyl)oxy-1-hydroxy-8(β)-methyl-2-[1(R*)-methyl]epoxyethenyl-4-oxo-4a(4H)-8,8a-epoxynaphthalenecarboxylate (152a). To a stirred solution of **145** (36 mg, 0.0852 mmol), 2,6-lutidine (10 μL, 0.0852 mmol), and *t*-butyl hydroperoxide (5.0~6.0 M in isooctane, 51μL, 0.256 mmol) in 1 mL of toluene was added solid vanadium oxyacetylacetonate (0.7 mg, 0.00256 mmol) at room temperature. After 2 d the mixture was passed through a short pad of silica gel with diethyl ether as eluent and the eluent was concentrated in vacuo. Column chromatography (hexane-ethyl acetate, 6:1 to 3:1) of the residue afforded 19.2 mg (53%) of **152a** and 6.8 mg (19%) of **152b**. Spectroscopic data for **152a**: IR (film) 3469, 1752, 1723, 1437, 1391, 1252, 1202, 1144, 1097, 910, 842, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.98 (d, J=9.6 Hz, 1H), 5.89 (dd, J=9.6, 6.2 Hz, 1H), 5.01 (d, J=6.1 Hz, 1H), 4.67 (ddd, J=4.5, 4.5, 1.7 Hz, 1H), 3.65 (s, 3H), 3.07 (d, J=4.5 Hz, 1H), 2.81 (d, J=4.4 Hz,



1H), 2.66 (m, 2H), 2.51 (ddd, J=15.3, 2.1, 2.1 Hz, 1H), 1.82 (ddd, J=14.2, 4.2, 2.5 Hz, 1H), 1.61 (s, 3H), 1.46 (s, 3H), 0.80 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 167.3, 133.9, 131.5, 69.0, 66.8, 64.6, 64.0, 58.5, 57.1, 53.4, 52.2, 43.2, 38.1, 25.6, 20.0, 17.8, 16.6, 04.0, -5.1; MS (CI) *m/z* (rel. intensity) 439 (M + 1, 43), 423 (42), 421 (100), 407 (49), 403 (40), 389 (87), 381 (50), 373 (44), 363 (57), 345 (37), 331 (36), 307 (85), 277 (58), 275 (82), 247 (42), 243 (50), 229 (71), 213 (42), 167 (33); HRMS *m/z* Calcd for $C_{22}H_{35}O_7Si$ (M + 1): 439.2152. Found: 439.2152.; Anal. Calcd. for $C_{22}H_{34}O_7Si$: C, 60.25; H, 7.81. Found: C, 60.10; H, 7.80.

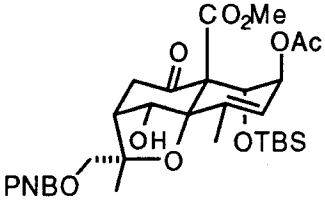
Spectroscopic data for **152b**; IR (film) 3474, 1753, 1723, 1253, 1200, 1096, 1064, 842, 814, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.99 (d, J=9.7 Hz, 1H), 5.90 (dd, J=9.7, 6.0 Hz, 1H), 5.00 (d, J=6.4 Hz, 1H), 4.51 (m, 1H), 3.68 (s, 3H), 2.95 (d, J=4.2 Hz, 1H), 2.67 (d, J=4.1 Hz, 1H), 2.63 (d, J=4.1 Hz, 1H), 2.32 (m, 3H), 1.63 (s, 3H), 1.52 (s, 3H), 0.79 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 167.3, 133.7, 131.6, 69.1, 67.2, 64.0, 63.8, 58.5, 56.6, 53.4, 51.1, 41.3, 36.0, 25.6, 21.1, 17.8, 16.7, -4.0, -5.1.

Methyl (1α,2β,6α,11R*)-2-Acetoxy-1-(*t*-butyldimethylsilyl)oxy-6,13-dihydroxy-9-oxo-(7βH)-5,11-epoxy-8-eudesmen-14-oate (161). A solution of **152b** (16.6 mg, 0.0379 mmol) in 1 mL of acetic acid was heated at 60 - 65 °C for 4 h. The mixture was cooled to room temperature and the volatile material was removed in vacuo. Column chromatography (hexane-ethyl acetate, 2:3 to 1:2) of the residue afforded 8.2 mg (44%) of **161**: IR (film) 3510, 3477, 1718, 11236, 1143, 1112, 1085, 1026, 992, 963, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.59 (d, J=4.3 Hz, 1H), 5.24 (d, J=2.0 Hz, 1H), 5.12 (s, 1H), 4.82 (s, 1H), 3.68 (s, 3H), 3.57 (d, J=11.5 Hz, 1H), 3.45



(d, J=11.5 Hz, 1H), 2.97 (dd, J=17.9, 3.3 Hz, 1H), 2.49 (dd, J=17.9, 4.3 Hz, 1H), 2.42 (m, 1H), 2.13 (s, 3H), 2.01 (s, 3H), 1.52 (s, 3H), 0.87 (s, 9H), 0.21 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 169.4, 168.2, 139.5, 123.4, 84.9, 84.6, 84.7, 72.7, 72.0, 69.8, 67.4, 52.8, 47.8, 44.0, 25.8, 24.3, 21.7, 21.0, 18.2, -4.3, -6.1; MS (CI) *m/z* (rel. intensity) 499 (M + 1, 16), 498 (M, 2), 481 (10), 441 (16), 440 (31), 439 (100), 425 (8), 424 (15), 423 (53), 422 (15), 421 (46), 407 (32), 405 (15), 403 (25), 391 (25), 382 (17), 381 (68), 367 (27), 349 (33), 307 (44), 289 (58), 275 (55), 257 (51), 243 (22), 233 (22), 231 (25), 229 (21), 177 (56), 141 (30), 133 (31); HRMS, *m/z* Calcd for $C_{24}H_{39}O_9Si$ (M + 1): 499.2363. Found: 499.2361.

Methyl (1α,2β,6α,11R*)-2-Acetoxy-1-(*t*-butyldimethylsilyl)oxy-6-hydroxy-13-*p*-nitrobenzoyloxy-9-oxo-(7βH)-5,11-epoxy-8-eudesmen-14-oate (162).

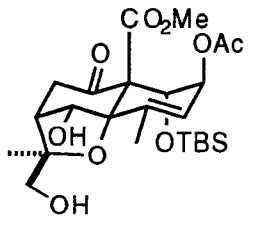


To a stirred solution of **161** (8 mg, 0.190 mmol), triethylamine (7 μL, 0.0481 mmol), and *p*-nitrobenzoyl chloride (6 mg, 0.0321 mmol) in 0.2 mL of methylene chloride was added a catalytic amount of N,N-dimethylaminopyridine (DMAP) at room temperature. After 6 h aqueous sodium bicarbonate was added and the mixture was extracted with diethyl ether (8 mL). The separated organic layer was dried and concentrated in vacuo. Column chromatography (hexane-ethyl acetate, 3:1 to 1:1) of the residue afforded 5 mg (55%) of **162** as a colorless solid: mp 213 - 214 °C; IR (film) 35011, 1728, 1529, 1349, 1273, 1264, 1259, 1235, 1142, 1110, 1017, 993, 840, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J=8.8 Hz, 2H), 8.17 (d, J=8.8 Hz, 2H), 5.63 (d, J=6.3 Hz, 1H), 5.24 (br. s, 2H), 4.79 (s, 1H), 4.30 (d, J=11.4 Hz, 1H), 4.25 (d, J=11.4 Hz, 1H), 3.69 (s, 3H), 2.81 (dd, J=16.0, 1.7 Hz, 1H), 2.60 (m, 2H), 2.15 (s, 3H), 2.02 (s, 3H), 1.66 (s, 3H), 0.85

(s, 9H), 0.20 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 169.6, 168.1, 163.9, 150.6, 138.9, 135.1, 130.6, 124.6, 124.6, 123.5, 85.6, 83.2, 82.8, 72.2, 70.2, 69.8, 52.9, 47.7, 43.6, 25.8, 24.9, 21.7, 21.0, 18.2, -4.4, -6.1; MS (CI) *m/z* (rel. intensity) 648 (M + 1, 13), 589 (17), 588 (47), 572 (17), 570 (34), 556 (14), 531 (11), 530 (23), 456 (35), 422 (11), 421 (32), 403 (14), 333 (16), 307 (14), 289 (35), 257 (14), 224 (19), 177 (100), 168 (35), 159 (15); HRMS *m/z* Calcd for $C_{31}H_{42}O_{13}NSi$ (M + 1): 648.2476. Found: 648.2476.

Compound **162** crystallized from octane-ethyl acetate in the space group P2(1)/c with a=13.361 (3) Å, b=13.611 (2) Å, c=18.573 (2) Å, β=91.57 (2)°, z=4 and d_{calcd}=1.306 g/cm^3. The intensity data were measured on a Siemens P4 diffractometer (Cu Kα radiation). There were 3118 unique reflections and the structure was solved by direct methods. The final discrepancy indices were R=0.0535 and Rw=0.0546.

Methyl (1α,2β,6α,11R*)-2-Acetoxy-1-(*t*-butyldimethylsilyl)oxy-6,13-dihydroxy-9-oxo-(7βH)-5,11-epoxy-8-eudesmen-14-oate (163). To a stirred solution of **149** (5.3 mg, 0.0110 mmol) in 0.3 mL of methylene chloride was added *m*-chloroperbenzoic acid (2.5 mg, 0.0121 mmol) at room temperature. After 3 d the mixture was diluted with diethyl ether (6 mL) and aqueous sodium bicarbonate solution and was stirred vigorously for 1 h. The organic layer was separated, dried and concentrated in vacuo to give crude **164** as a 1:1 mixture of stereoisomers based on ^1H NMR analysis.

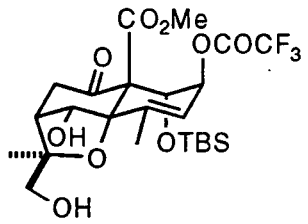


Crude mixture **164** was dissolved in 0.5 mL of deuterated chloroform in a NMR tube. After 5 h the mixture was concentrated in vacuo and the residue was purified by column chromatography (hexane-ethyl acetate, 5:1 to 1:2) to give 1.5 mg (28%) of **163** and 1.9 mg (36%) of recovered **164b**. Spectroscopic

data for **163**: IR (film) 3321, 1740, 1723, 1375, 1230, 1113, 1020, 980, 968, 839, 781 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.51 (m, 1H), 5.31 (m, 1H), 5.05 (s, 1H), 4.88 (d, J=2.7 Hz, 1H), 3.68~3.64 (2H), 3.67 (s, 3H), 2.80 (dd, J=18.7, 3.0 Hz, 1H), 2.70 (dd, J=18.7, 4.1 Hz, 1H), 2.06 (m, 5H), 1.20 (s, 3H), 0.83 (s, 9H), 0.19 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 170.2, 168.2, 138.3, 126.6, 86.0, 83.9, 80.3, 75.0, 73.3, 70.7, 69.6, 52.9, 47.7, 44.8, 25.9, 22.2, 21.7, 18.3, -4.3, -5.9; MS (CI) *m/z* (rel. intensity) 499 (M + 1, 43), 481 (10), 467 (9), 440 (19), 439 (66), 423 (35), 421 (58), 407 (31), 405 (16), 391 (28), 389 (38), 381 (32), 349 (33), 307 (45), 289 (100), 275 (33), 259 (15), 257 (39), 243 (18), 233 (19), 177 (75); HRMS *m/z* Calcd for $C_{24}H_{39}O_9Si$ (M + 1): 499.2363. Found: 499.2361.

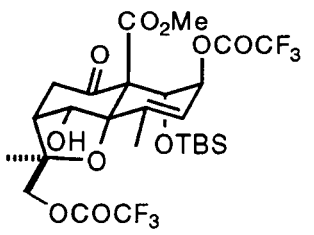
Spectroscopic data for **164b**: IR (film) 3529, 3384, 1735, 1439, 1370, 1232, 1152, 1132, 1104, 1071, 1022, 971, 942, 839, 786, 736 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 5.72 (s, 1H), 5.34 (d, J=1.6 Hz, 2 H), 5.26 (m, 1H), 4.89 (m, 1H), 3.48 (d, J=10.6 Hz, 1H), 3.06 (s, 3H), 2.55 (m, 4H), 2.35 (s, 3H), 2.17 (s, 3H), 1.54 (s, 3H), 0.92 (s, 9H), 0.46 (s, 3H), 0.42 (s, 3H); MS (CI) *m/z* (rel. intensity) 499 (M + 1, 10), 483 (10), 481 (18), 441 (9), 439 (30), 423 (23), 422 (27), 421 (98), 405 (19), 403 (64), 349 (10), 307 (11), 289 (24), 257 (18), 181 (16), 153 (100); HRMS *m/z* Calcd for $C_{24}H_{39}O_9Si$ (M + 1): 499.2363. Found: 499.2361.

Methyl (1α,2β,6α,11R*)-1-(*t*-Butyldimethylsilyl)oxy-6,13-dihydroxy-(7βH)-5,11-epoxy-9-oxo-2-trifluoroacetoxy-8-eudesmen-14-oate (165). To a



stirred solution of **152a** (16.5 mg, 0.0376 mmol) in 0.4 mL of deuterated chloroform in a NMR tube was added trifluoroacetic acid (4.4 μL, 0.0564 mmol) at room temperature. After 30 min the reaction was complete as determined by ^{1}H NMR analysis. The mixture was diluted with diethyl ether and washed with aqueous sodium bicarbonate. The separated organic layer was dried and concentrated in vacuo. Column chromatography (hexane-ethyl acetate, 2:1 to 1:1) of the residue afforded 11.5 mg (55%) of **165**: IR (film) 3292, 1782, 1721, 1379, 1221, 1151, 1115, 1039, 966, 934, 840, 779 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (s, 1H), 5.46 (br.s, 1H), 5.04 (s, 1H), 4.95 (d, J=1.9 Hz, 1H), 3.73 (d, J=11.7 Hz, 1H), 3.69 (d, J=11.7 Hz, 1H), 3.67 (s, 3H), 2.81 (dd, J=18.5, 2.9 Hz, 1H), 2.72 (dd, J=18.5, 3.9 Hz, 1H), 2.49 (t, J=3.5 Hz, 1H), 2.12 (s, 3H), 1.20 (s, 3H), 0.83 (s, 9H), 0.18 (s, 3H), 0.09 (s, 3H); MS (CI) *m/z* (rel. intensity) 553 (M + 1, 1), 440 (1), 439 (4), 423 (2), 381 (2), 307 (1), 289 (7), 177 (14), 133 (5), 129 (5), 115 (100); HRMS, *m/z* Calcd for $C_{24}H_{37}F_3O_9Si$ (M + 1): 553.2080. Found: 553.2078.

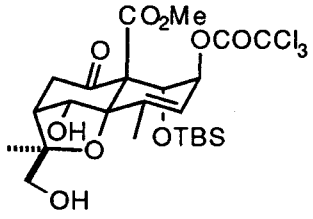
Methyl (1α,2β,6α,11R*)-1-(*t*-Butyldimethylsilyl)oxy-6-hydroxy-(7βH)-5,11-epoxy-9-oxo-2,12-di-trifluoroacetoxy-8-eudesmen-14-oate (167). To a



solution of **152a** (5.6 mg, 0.0128 mmol) in 0.4 mL of deuterated chloroform in a NMR tube was added trimethylsilyl trifluoroacetate (6 μL, 0.035 mmol) at room temperature. After 24 h the mixture was concentrated in vacuo and the residue was purified by column chromatography (hexane-ethyl acetate, 2:1 to 1:1) to give 4.0 mg (48%) of **167**:

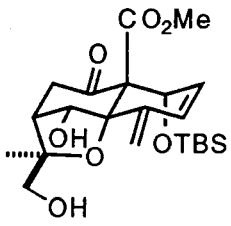
IR (film) 3540, 1784, 1721, 1222, 1149, 995, 933, 840, 778, 733 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (m, 1H), 5.28 (m, 1H), 5.18 (br.s, 1H), 4.82 (t, J=1.6 Hz, 1H), 4.75 (d, J=10.6 Hz, 1H), 4.62 (d, J=10.6 Hz, 1H), 3.67 (s, 3H), 2.79 (dd, J=17.6, 2.8 Hz, 1H), 2.57 (dd, J=17.6, 4.0 Hz, 1H), 2.50 (t, J=3.0 Hz, 1H), 2.13 (t, J=1.5 Hz, 1H), 1.26 (s, 3H), 0.83 (s, 9H), 0.17 (s, 3H), 0.10 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$, reference to trifluoromethyltoluene) δ -75.92, -76.29; MS (CI) *m/z* (rel. intensity) 591 (5), 563 (5), 537 (12), 536 (34), 535 (M - F_3CCO_2, 97), 520 (12), 519 (35), 518 (14), 517 (44), 503 (13), 478 (19), 477 (63), 421 (39), 403 (39), 389 (12), 385 (19), 289 (41), 271 (8), 257 (12), 178 (13), 177 (89), 115 (100); HRMS, *m/z* Calcd for $C_{24}H_{34}F_3O_8Si$ (M - F_3CCO_2): 535.1975. Found: 535.1976.

Methyl (1α,2β,6α,11R*)-1-(*t*-Butyldimethylsilyl)oxy-6,13-dihydroxy-(7βH)-5,11-epoxy-9-oxo-2-trichloroacetoxy-3-eudesmen-14-oate (166). To a solution of **152a** (13.2 mg, 0.030 mmol) in 0.4 mL of deuterated chloroform in a NMR tube was added a solution of trichloroacetic acid (1M in chloroform, 45 μL, 0.045 mmol) at room temperature. After 2.5 h the reaction was complete as dertermined by ^{1}H NMR analysis. The mixture was diluted with ethyl acetate (8 mL) and washed with aqueous sodium bicarbonate. The separated organic layer was dried and concentrated in vacuo. Column chromatography (hexane-ethyl acetate, 2:1 to 1:1) of the residue afforded 12 mg (67%) of **166**: IR (film) 3290, 3230, 1760, 1720, 1233, 1151, 1113, 1037, 986, 934, 915, 838, 779, 733, 680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.52 (m, 1H), 5.44 (m, 1H), 5.01 (s, 1H), 4.98 (m, 1H), 3.68~3.71 (2H), 3.70 (s, 3H), 2.81 (dd, J=18.6, 3.0 Hz, 1H), 2.73 (dd, J=18.6, 4.0 Hz, 1H), 2.13 (t, J=1.6 Hz, 3H), 1.20 (s, 3H), 0.85 (s, 9H), 0.20 (s,



3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 167.8, 161.4, 140.7, 123.4, 85.4, 84.5, 80.8, 80.0, 72.6, 70.3, 69.8, 53.3, 47.6, 44.9, 25.9, 22.2, 22.1, 18.3, -4.2, -6.2; MS (CI) *m/z* (rel. intensity) 601 (M + 1, 3), 479 (2), 475 (4), 439 (M - Cl_3CCO_2, 33), 425 (10), 423 (14), 421 (21), 407 (22), 391 (9), 390 (8), 389 (27), 381 (29), 363 (9), 307 (16), 290 (12), 289 (65), 275 (13), 257 (19), 231 (12), 178 (11), 177 (100); HRMS, *m/z* Calcd for $C_{22}H_{35}O_7Si$ (M - Cl_3CCO_2): 439.2152. Found: 439.2152.

Methyl (1α,6α,11S*)-1-(*t*-Butyldimethylsilyl)oxy-6,13-dihydroxy-(7βH)-5,11-epoxy-9-oxo-2,4(15)-eudesmadien-14-oate (169). To a stirred solution of

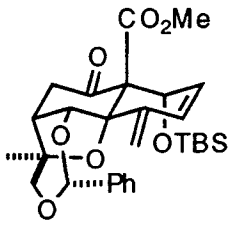


152a (126 mg, 0.287 mmol) in 3 mL of toluene was added neat titanium tetraisopropoxide (257 μL, 0.862 mmol) at room temperature. After 19 h the mixture was cooled to 0 °C, diluted with diethyl ether (10 mL) and 1N sulfuric acid, and stirred vigorously until the mixture became clear. The organic layer was separated, washed with saturated sodium bicarbonate solution and concentrated in vacuo to give crude **168**: ^1H NMR (300 MHz, C_6D_6) δ 6.52 (s, 1H), 6.20 (d, J=9.8 Hz, 1H), 5.61 (dd, J= 9.8, 5.8 Hz, 1H), 5.40 (d, J=5.8 Hz, 1H), 5.12 (m, 2H), 3.90 (d, J=10.3 Hz, 1H), 3.05 (d, J=16.6 Hz, 1H), 3.00 (s, 3H), 2.52 (m, 1H), 2.47 (d, J=4.5 Hz, 1H), 2.32 (d, J=4.5 Hz, 1H), 2.17 (ddd, J=16.6, 6.2, 3.4 Hz, 1H), 1.37 (s, 3H), 0.98 (d, J=4.4 Hz, 1H), 0.81 (s, 9H), 0.20 (s, 3H), 0.04 (s, 3H).

Crude **168** was dissolved in a 0.1% hydrochloric acid solution in chloroform at room temperature. After 15 min the mixture was diluted with diethyl ether, washed with saturated sodium bicarbonate solution and with saturated brine, and concentrated in vacuo to give 92 mg (73%) of **169**: IR (film) 3291, 1742, 1714, 1468, 1381, 1250, 1166, 1111, 1083, 1035, 995, 916, 841,

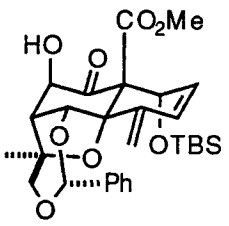
779, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.26 (s, 1H), 6.19 (d, J=10.1 Hz, 1H), 5.84 (dd, J=10.1, 4.7 Hz, 1H), 5.20 (s, 2H), 4.92 (d, J=4.8 Hz, 1H), 3.66 (d, J=12.5 Hz, 1H), 3.63 (s, 3H), 3.58 (d, J=12.5 Hz, 1H), 2.95 (dd, J=8.9, 4.1 Hz, 1H), 2.83 (dd, J=8.9, 2.3 Hz, 1H), 2.49 (t, J=3.3 Hz, 1H), 1.20 (s, 3H), 0.88 (s, 9H), 0.18 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 168.4, 138.5, 129.7, 128.7, 118.4, 84.9, 84.2, 77.6, 70.8, 69.8, 68.8, 53.0, 48.9, 45.1, 26.1, 22.6, 18.3, -4.3, -5.4; MS (CI) *m/z* (rel. intensity) 439 (M + 1, 35), 423 (75), 389 (25), 381 (64), 335 (15), 307 (24), 289 (80), 257 (23), 177 (100); HRMS *m/z* Calcd for $C_{22}H_{35}O_7Si$ (M + 1): 439.2152. Found: 439.2152.

Acetal 170. To a stirred solution of **169** (30 mg, 0.0684 mmol) and benzaldehyde dimethyl acetal (52 μL, 0.342 mmol) in 1 mL of methylene chloride was added solid pyridinium *p*-toluenesulfonate (1 mg, 0.004 mmol) at room temperature. After 24 h an additional quantity of benzaldehyde dimethyl acetal (52 μL, 0.342 mmol) was added and stirring was continued for 24 h. The mixture was concentrated in vacuo and the residue was purified by column chromatography (hexane-ethyl acetate, 9:1 to 1:2) to give 25 mg (70%) of **170** as a single diastereomer: IR (film) 1742, 1713, 1251, 1223, 1175, 1124, 1086, 1031, 1003, 912, 839, 778, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.36 (m, 3H), 6.22 (d, J=9.9 Hz, 1H), 6.11 (s, 1H), 5.83 (dd, J=10.0, 4.9 Hz, 1H), 5.76 (s, 1H), 5.75 (s, 1H), 5.21 (s, 1H), 4.95 (d, J=4.9 Hz, 1H), 3.83 (d, J=12.6 Hz, 1H), 3.60 (s, 3H), 3.47 (d, J=12.6 Hz, 1H), 3.12 (t, J=3.5 Hz, 1H), 2.94 (d, J=3.6 Hz, 1H), 1.29 (s, 3H), 0.89 (s, 9H), 0.18 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2, 168.5, 139.1, 138.3, 130.4, 128.6, 128.3, 126.2, 118.6, 99.8, 84.6, 84.4, 82.4, 76.7, 71.4, 69.4, 53.0, 43.2, 41.4, 26.1, 20.1, 18.4, -4.2, -5.3; MS (CI) *m/z* (rel. intensity) 527 (M + 1,



40), 512 (12), 511 (35), 470 (15), 469 (47), 450 (10), 449 (35), 421 (25), 405 (28), 395 (42), 317 (25), 289 (100); HRMS *m/z* Calcd for $C_{29}H_{39}O_7Si$ (M + 1): 527.2465. Found: 527.2462.

Ketol 171. To a stirred solution of **170** (82 mg, 0.156 mmol) in 1 mL of



tetrahydrofuran was added dropwise sodium hexamethyldisilazide (1M in THF, 171 μL, 0.171 mmol) at -78 °C. After 30 min a solution of *trans*-2-(phenylsulfonyl)-3-phenyloxaziridine (64 mg, 0.234 mmol) in 1 mL of tetrahydrofuran was added and the resulting mixture was stirred for 30 min. The mixture was quenched by the addition of 200 μL of water and 200 μL of triethylamine at -78 °C and was allowed to warm to room temperature. After 20 min with vigorous stirring the mixture was extracted with diethyl ether (10 mL) and the separated organic layer was concentrated in vacuo. Column chromatography (hexane-ethyl acetate, 3:1) of the residue afforded 58 mg (70%) of **171** as a colorless solid: IR (film) 3435, 1736, 1250, 1222, 1169, 1128, 1084, 1044, 1005, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.36 (m, 3H), 6.22 (d, J=10.0 Hz, 1H), 6.11 (s, 1H), 5.88 (s, 1H), 5.81 (dd, J=10.0, 4.6 Hz, 1H), 5.75 (s, 1H), 5.19 (s, 1H), 5.03 (d, J=4.5 Hz, 1H), 4.36 (t, J=2.5 Hz, 1H), 3.82 (d, J=12.6 Hz, 1H), 3.62 (s, 3H), 3.52 (d, J=12.6 Hz, 1H), 3.17 (d, J=1.6 Hz, 1H), 2.94 (d, J=2.9 Hz, 1H), 1.33 (s, 3H), 0.87 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 168.4, 138.9, 138.3, 131.0, 128.6, 128.2, 127.6, 126.2, 118.5, 100.2, 84.4, 82.9, 79.9, 74.6, 71.3, 70.2, 53.2, 48.2, 26.0, 19.6, 18.4, -4.3, -5.0; MS (CI) *m/z* (rel. intensity) 543 (M + 1, 23), 465 (11), 437 (13), 412 (8), 411 (31), 379 (11), 363 (11), 333 (11), 306 (14), 305 (80), 287 (21), 273 (8), 213 (16), 177 (76), 163 (25), 135 (12), 133 (26), 107 (100); HRMS *m/z* Calcd for $C_{29}H_{39}O_8Si$ (M + 1): 543.2414.

Found: 543.2413.; Anal. Calcd for $C_{29}H_{38}O_8Si$: C, 64.18; H,7.06. Found: C, 63.79; H,6.97.

Methyl (1α,6α,8β,11S*)-1-(*t*-Butyldimethylsilyl)oxy-(7βH)-5,11-epoxy-9-oxo--6,8,13-trihydroxy-2,4(15)-eudesmadien-14-oate (172). To a stirred solution of **169** (26 mg, 0.0593 mmol) in 1.5 mL of tetrahydrofuran was added dropwise sodium hexamethyldisilazide (1M in THF, 190 μL, 0.190 mmol) at -78 °C. After 30 min a solution of *trans*-2-(phenylsulfonyl)-3-phenyloxaziridine (24 mg, 0.089 mmol) in 1 mL of tetrahydrofuran was added slowly and stirring was continued for 30 min. The mixture was quenched with saturated aqueous ammonium chloride solution and was extracted with diethyl ether (7 mL x 2). The separated organic layer was dried and concentrated in vacuo. Column chromatography (hexane-ethyl acetate, 2:1 to 1:1) of the residue afforded 19 mg (70%) of **172**: IR (film) 3427, 3370, 3338, 1721, 1250, 1229, 1111, 1034, 1000, 915, 778, 732 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 6.31 (s, 1H), 6.20 (d, J=10.3 Hz, 1H), 5.79 (dd, J=10.4, 4.8 Hz, 1H), 5.43 (s, 1H), 5.24 (s, 1H), 4.96 (d, J=4.8 Hz, 1H), 4.28 (d, J=3.0 Hz, 1H), 3.64 (s, 5H), 2.60 (d, J=3.0 Hz, 1H), 1.18 (s, 3H), 0.86 (s, 9H), 0.16 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 168.6, 139.0, 130.8, 127.7, 119.0, 84.7, 82.6, 75.6, 74.2, 70.6, 70.1, 69.3, 54.8, 53.3, 26.1, 22.0, 18.4, -4.3, -5.2; MS (CI) *m/z* (rel. intensity) 455 (M + 1, 3), 426 (6), 425 (22), 407 (11), 382 (7), 381 (29), 305 (19), 289 (10), 275 (11), 231 (13), 178 (12), 177 (100), 133 (16); HRMS *m/z* Calcd for $C_{22}H_{35}O_8Si$ (M + 1): 455.2101. Found: 455.2102.

***trans* Diol 175.** To a stirred solution of **171** (10 mg, 0.0184 mmol) in 1mL of methanol was added solid sodium borohydride (5 mg, 0.133 mmol) at room temperature. After 30 min the mixture was diluted with diethyl ether (10 mL) and washed with 0.1 M hydrochloric acid solution. The separated organic layer was washed with saturated sodium bicarbonate solution, dried, and concentrated. Column chromatography (hexane-ethyl acetate, 4:1 to 2:1) of the residue afforded 4.6 mg (46%) of **175**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.34 (m, 3H), 6.24 (d, J=10.0 Hz, 1H), 6.14 (s, 1H), 5.85 (dd, J=10.0, 5.1 Hz, 1H), 5.69 (s, 1H), 5.59 (s, 1H), 5.19 (s, 1H), 5.12 (d, J=5.1 Hz, 1H), 4.53 (d, J=9.5 Hz, 1H, OH), 4.36 (d, J=5.0 Hz, 1H), 4.31 (dd, J=9.5, 5.1 Hz, 1H), 3.79 (d, J=12.9 Hz, 1H), 3.61 (s, 3H), 3.50 (d, J=12.9 Hz, 1H), 2.95 (s, 1H), 2.42 (br. s, 1H, OH), 1.46 (s, 3H), 0.94 (s, 9H), 0.23 (s, 3H), 0.16 (s, 3H).

Imidazolide 176. A solution of **175** (4.6 mg, 0.00848 mmol) and carbonyldiimidazole (3 mg, 0.0170 mmol) in 0.3 mL of toluene was heated at 60 - 65 °C for 3 h. After cooling to room temperature, the mixture was purified by column chromatography (hexane-ethyl acetate, 6:1 to 1:1) to give 3.7 mg (69%) of **176** as a colorless solid: IR (film) 3276, 1764, 1731, 1391, 1289, 1243, 1175, 1136, 1114, 1091, 1042, 1003, 975, 918, 837, 775, 753 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.48 (m, 3H), 7.35 (m, 3H), 7.12 (s, 1H), 6.29 (d, J=10.0 Hz, 1H), 6.17 (s, 1H), 5.60 (dd, J=10.0, 4.9 Hz, 1H), 5.66 (s, 1H), 5.64 (s, 1H), 5.26 (s, 1H), 5.13 (d, J=5.1 Hz, 1H), 4.84 (d, J=9.4 Hz, 1H), 4.63 (dd, J=9.4, 5.3 Hz, 1H), 3.83 (d, J=12.8 Hz, 1H), 3.65 (s, 3H), 3.55 (d, J=12.8 Hz, 1H), 3.12 (s, 1H), 1.63 (s, 3H), 0.96 (s, 9H), 0.25 (s, 3H), 0.18 (s, 3H); MS (CI) *m/z* (rel.

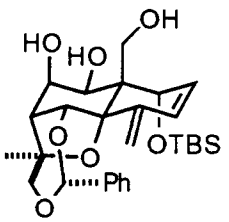
intensity) 571 (5), 507 (M - C_4H_9OSi, 10), 475 (8), 429 (8), 405 (15), 402 (12), 401 (49), 395 (24), 364 (6), 363 (18), 317 (10), 290 (18), 289 (100), 271 (17), 243 (6), 229 (6), 183 (13), 177 (42), 163 (17), 133 (27), 117 (24), 115 (27), 107 (75), 97 (56); HRMS *m/z* Calcd for $C_{27}H_{27}N_2O_8$ (M - C_4H_9OSi): 507.1767. Found: 507.1769.

Compound **176** crystallized from octane in the space group P-1 with a=8.866 (2) Å, b=11.007 (2) Å, c=18.616 (4) Å, α=73.86 (3)°, β=93.77 (2)°, γ=73.02 (3)°, z=2 and d_{calcd}=1.272 g/cm^3. The intensity data were measured on a Siemens P4 diffractometer (Cu Kα radiation). There were 3174 unique reflections and the structure was solved by direct methods. The final discrepancy indices were R=0.0750 and Rw=0.0730.

***cis* Diol 177.** To a stirred solution of **171** (40 mg, 0.0737 mmol) in 2 mL of tetrahydrofuran was added neat titanium tetraisopropoxide (66 mL, 0.221 mmol) at room temperature. After 15 min the mixture was cooled to -78 °C and solid sodium borohydride (8.4 mg, 0.221 mmol) was added. The mixture was stirred for 1.5 h at -78 °C and warmed to room temperature, and stirring was continued for 30 min. The residual sodium borohydride was destroyed with a few drops of acetone and the mixture was concentrated in vacuo. The residue was passed through a short pad of silica gel with ethyl acetate as eluent, and the concentrated eluent was purified by column chromatography (hexane-ethyl acetate, 2:1 to 1:1) to give 18 mg (49%) of **177**: IR (film) 3473, 3454, 1719, 1460, 1455, 1382, 1306, 1252, 1217, 1130, 1107, 1073, 1025, 963, 912, 864, 838, 777, 731, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.33 (m, 3H), 6.28 (s, 1H), 6.22 (dd, J=10.0, 5.0 Hz, 1H), 5.71 (s, 1H), 5.21 (s, 1H), 5.00 (t, J=10.1 Hz, 1H), 4.74 (s, 1H), 4.42 (d, J=4.9 Hz, 1H), 4.29 (dd,

J=9.8, 3.1 Hz, 1H), 3.71 (d, J=12.6 Hz, 1H), 3.62 (s, 3H), 3.44 (d, J=12.6 Hz, 1H), 3.14 (d, J=3.0 Hz, 1H), 3.10 (d, J=11.2 Hz, 1H, OH), 2.65 (br.s, 1H, OH), 1.53 (s, 3H), 0.94 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 138.9, 138.8, 132.4, 128.5, 128.2, 126.1, 125.8, 121.1, 99.6, 85.3, 84.8, 83.4, 78.1, 75.5, 71.2, 66.8, 61.0, 52.5, 47.2, 25.9, 18.5, 18.2, -4.2, -4.9; MS (CI) *m/z* (rel. intensity) 545 (M + 1, 36), 544 (M, 6), 529 (9), 487 (14), 469 (5), 467 (10), 439 (13), 423 (26), 421 (15), 413 (19), 395 (13), 381 (17), 290 (10), 289 (57), 271 (11), 178 (11), 177 (100), 117 (14), 107 (48); HRMS, *m/z* Calcd for $C_{29}H_{41}O_8Si$ (M + 1): 545.2570. Found: 545.2571.

Triol 178. To a stirred solution of **171** (34.2 mg, 0.0630 mmol) in 1.5 mL of tetrahydrofuran was added titanium tetraisopropoxide (28 μL, 0.0945 mmol) at room temperature. After 30 min the mixture was cooled to -78 °C and a solution of lithium aluminum hydride (1 M in toluene, 252 μL, 0.252 mmol) was added dropwise. Stirring was continued for 30 min and the mixture was warmed to -25 °C. After 6 h at -25 °C an additional quantity of lithium aluminum hydride (1 M in toluene, 100 μL, 0.1 mmol) was added and the mixture was stirred for 12 h at this temperature. The mixture was re-cooled to -78 °C and quenched by sequential addition of 0.1 mL of ethyl acetate, 0.35 mL of methanol, and solid sodium borohydride (25 mg, 0.95 mmol). The mixture was warmed to 0 °C and diluted with 10 mL of diethyl ether, and 10 mL of 1N sulfuric acid solution was added slowly. After 30 min of vigorous stirring the organic layer was separated and the aqueous layer was extracted with diethyl ether (10mL X 2). The combined organic layer was washed with saturated sodium bicarbonate solution and concentrated in vacuo. Column chromatography (hexane-ethyl acetate, 2:1 to 1:1) of the residue afforded 16



mg (50%) of **178**: IR (film) 3425, 3396, 1461, 1380, 1253, 1164, 1135, 1088, 1070, 1028, 924, 858, 839, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.34 (m, 3H), 6.45 (s, 1H), 6.15 (d, J=10.0 Hz, 1H), 5.70 (m, 2H), 5.33 (s, 1H), 5.04 (m, 2H), 4.38 (br. dd, J=9.4, 5.7 Hz, 1H), 4.32 (d, J=5.5 Hz, 1H), 3.72 (d, J=12.5 Hz, 1H), 3.63 (br. dd, J=11.9, 5.5 Hz, 1H), 3.43 (m, 3H), 3.11 (d, J=3.4 Hz, 1H), 2.60 (br. d, 2H, OH), 2.41 (br. s, 1H, OH), 1.50 (s, 3H), 0.94 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 138.9, 133.4, 128.4, 128.2, 126.1, 125.5, 124.6, 99.2, 84.4, 81.9, 78.2, 76.2, 73.2, 67.8, 66.4, 51.1, 48.3, 26.0, 19.1, 18.3, -4.2, -4.4; MS (CI) *m/z* (rel. intensity) 517 (M + 1, 5), 411 (13), 395 (8), 385 (12), 367 (9), 337 (10), 319 (8), 307 (7), 289 (14), 261 (21), 249 (10), 232 (9), 231 (58), 213 (24), 163 (11), 161 (14), 133 (57), 117 (44), 115 (49), 107 (100); HRMS, *m/z* Calcd for $C_{28}H_{41}O_7Si$ (M + 1): 517.2622. Found: 517.2619.

Bibliography

1. Kupchan, S. M.; Komoda, Y.; Court, W. A.; Thomas, G. J.; Smith, P. M.; Gilmore, C. J.; Haltiwanger, R. C.; Bryan, R. S. *J. Am. Chem. Soc.* **1972**, *94*, 1354.
2. Kupchan, S. M.; Court, W. A.; Daily, R. G.; Gilmore, C. J.; Bryan, R. S. *J. Am. Chem. Soc.* **1972**, *94*, 7194.
3. Smith, R. M. *The Alkaloids* ; Manske, R. H. F. Ed.; Academic Press; New York, 1977, Vol. 16, pp 215-248.
4. Crombie, L.; Crombie, W. M. L.; Whiting, D. A. *The Alkaloids*; Manske, R. H. F. Ed.; Academic Press; New York, 1990, Vol. 39, pp 139-164.
5. Crombie, L.; Toplis, D.; Whiting, D. A.; Rozsa, Z.; Hofmann, J.; Szendrei, K. *J. Chem.Soc. Perkin Trans.I*, **1986**, 531.
6. Getahun, A.; Kriokorian, A. D. *Econ. Bot.* **1973**, *27*, 353.
7. Legras, M.; Fretillere, Y. *Med. Trop.* **1965**, *25*, 720.
8. Baxter, R. L.; Crombie, L.; Simmonds, D. J.; Whiting, D. A.; Braenden, O. J.; Szendrei, K. *J. Chem Soc. Perkin Trans.I*, **1979**, 2965.
9. Fluckiger, F.; Gerock, *J. Pharmac. J. Trans.* **1887**, *18*, 221.
10 Wolfes, O. *Arch. Pharm.* **1930**, *268*, 81.
11. Von Bruche, F. *Arch. exp. Path. Pharmak.* **1941**, *198*, 100.
12. Szendrei, K. *Bull. Narc.* **1980**, *32*, 5.
13. Schorono, X.; Brenneisen, R.; Steingger, E. *Pharm. Acta Helv.* **1982**, *57*, 168.
14. (a) Kalix, P. *Pharmac. Ther.* **1990**, *48*, 397. (b) Kalix, P. *Pharmac & Toxicol.* **1992**, *70*, 77.
15. (a)Sugiura, K.; Yamada, K.; Hirata, Y. *Tetrahedron Lett.* **1973**, 113. (b) Pailer, M.; Streicher, W.; Leitch, *J. Monatsh. Chem.* **1971**, *102*, 1873.

16. Sasaki, K.; Hirata, Y. *J. Chem. Soc. Perkin Trans.II* **1972**, 1268.

17. Shizuri, Y.; Wada, H.; Sugiura, K.; Yamda, K.; Hirata, Y. *Tetrahedron* **1973**, *29*, 1795.

18. Taylor, I. F. Jr.; Watson, W. H. *Acta Cryst.* **1977**, *B33*, 3176.

19. Baxter, R. L.; Crombie, L.; Simmonds, D. J.; Whiting, D. A. *J. Chem Soc. Perkin Trans.I*, **1979**, 2972.

20. Crombie, L.; Crombie, W. M. L.; Crombie, L.; Whiting, D. A. *J. Chem Soc. Perkin Trans.I*, **1979**, 2976.

21. Baxter, R. L.; Crombie, W. M. L.; Crombie, L.; Simmonds, D. J.; Whiting, D. A. *J. Chem.Soc. Perkin Trans.I*, **1979**, 2982.

22. Kim, T.-S.; White, J. D. *Tetrahedron Lett.* **1993**, *34*, 5535.

23. Kubo,I.; Kim, M.; De Boer, G. *J. Chromatogr.* **1987**; *402*, 354

24. Kolb, H. C.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc. Perkin Trans.I*, **1992**, 2735. and references cited therein.

25. Sugiura, K.; Shizuri, Y.; Wada, H.; Yamada, K.; Hirata, Y. *Tetrahedron Lett.* **1971**, 2733.

26. Sousa, J. R.;Pinheiro, J. A.; Ribeiro, E. F.; Souza, E.; Maia, J. G. S. *Phytochemistry* **1986**, *25*, 1776.

27. Chunquan, C.; Jikai, L.; Dagang, W. *Phytochemistry* **1992**, *31*, 4391.

28. Han, B. H.; Park, M. M.; Ryu, J. R.; Park, J. H.; Naoki, H. *Phytochemistry* **1990**, *29*, 2303.

29. (a) Beroza, M. *J. Am. Chem. Soc.* **1951**, *73*, 3656. (b) Beroza, M. *J. Am. Chem. Soc.* **1953**, *75*, 44. (c) Beroza, M. *J. Org. Chem.* **1963**, *28*, 3562.

30. Acree, F. Jr.; Haller, H. L. *J. Am. Chem. Soc.* **1950**, *72*, 1608.

31. DelleMonache, F.; Bettlo; J. B, Marini; Bernays, E. A. *Z. Angew. Entomol.* **1984**, *97*, 406.

32. Shizuri, Y.; Yamada, K.; Hirata, Y. *Tetrahedron Lett.* **1973**, 741.

33. (a) Wu, D. G.; Liu, L.; Chen, K.-C. *Acta Bot. Yunnanica* **1987**, *3*, 471. (b) Wu, D. G. *Acta Bot. Yunnanica* **1986**, *8*, 343.

34. He, Z.-S.; Hong, S.-H.; Li, Y.; Sha, H.; Yu, X.-G. *Acta Chim. Sin.* **1987**, *45*, 510.

35. Sugiura, K.; Yamada, K.; Hirata, Y. *Tetrahedron Lett.* **1973**, 113.

36. He, Z.-S.; Hong, S.-H. Li, Y.; Sha, H.; Yu, X.-G. *Acta Chim. Sin.* **1985**, *43*, 593.

37. Li, Y.; Strutz, G. M.; Calhoun, L. A. *Can. J. Chem.* **1990**, *68*, 371.

38. Kuo, Y.-H.; Chen, C.-H.; Kuo, L.-M.; King, M.-L.; Wu, T.-S.; Lu, S.-T.; Chen, I.-S.; McPhail, D. R.; McPhail, A. T.; Lee, K.-H. *Heterocycles* **1989**, *29*, 1465

39. Kuo, Y.-H.; Chen, C.-H.; Kuo, L.-M. Y.; King, M.-L.; Wu, T.-S.; Haruna, M.; Lee, K.-H. *J. Nat. Prod.* **1990**, *53*, 422.

40. (a) Huffman, J. W.; Desai, R. C.; Hillenbrand, G. F. *J. Org. Chem.* **1984**, *49*, 982. (b) Huffman, J. W.; Raveendranath, P. C. *J. Org. Chem.* **1986**, *51*, 2148. (c) Huffman, J. W.; Raveendranath, P. C. *Tetrahedron* **1987**, *43*, 5557.

41. Sugiura, K.; Yamada, K.; Hirata, Y. *Chem. Lett.* **1975**, 579.

42. Maclean, J. D. B.; Holland, H. L. *Can. J. Chem.* **1986**, 64, 1031.

43. Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175.

44. Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1984**, *25*, 5953.

45. (a) Goldsmith, D. J.; Kwong, C. *J. Org. Chem.* **1978**, *43*, 3182 (b) Kraus, G. A.: Taschner, M. J. J. Org. Chem. *J. Org. Chem.* **1980**, *45*, 1175. (c) Bhakuni, D. S. *Pure & Appl. Chem.* **1990**, 1389

46. Schlessinger, R. H.; Bebernitz, G. R.; Lin, P.; Poss, A. T. *J. Am. Chem. Soc.* **1985**, *107*, 1777

47. Kienzle, F.; Stadlwieser, J.; Rank, W.; Schonholzer, P. *Helv. Cheim. Acta* **1990**, *73*, 1108.

48. Barton, D. H. R.; Cookson, R. C. *Quart. Rev.* **1956**, *10*, 44.

49. Zavada, J.; Krupicka, J.; Sicher, *J. Coll. Czech. Chem. Comm.* **1968**, *33*, 1393.

50. Greenwood, T. L.; Kellert, M. D.; Sedlock, J. *Org. Syn. Coll. Vol 4*, **1963**, 108

51. (a) Wolff, S.; Huecas, M. E.; Agosta, W. C. *J. Org. Chem.* **1982**, 47, 4358. (b) Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5574

52. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

53. Gemal, A. L.; Luche, J. L. *J. Org. Chem.* **1979**, *44*, 4187.

54. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

55. (a) Schuster, R. E.; Bennett, R. D. *J. Org. Chem.* **1973**, *38*, 2309. (b) Fratiello, A.; Stover, C. S. *J. Org. Chem.* **1975**, *40*, 1244.

56. (a) Lipshutz, B. H. *Synthesis* **1987**, 325. (b) Lipshultz, B. H.; Parker, D. A.; Kozlowski, J. A.; Nguyen, S. L. *Tetrahedron Lett.* **1984**, *25*, 5959. (c) Lipshultz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928.

57. Reviews ; (a) Clennan, E. L. *Tetrahedron* **1991**, *47*, 1343. (b) Wasserman, H. H.; Ives, J. L. *Tetrahedron* **1981**, *37*, 1825. (c) Balci, M. *Chem. Rev.* **1981**, *81*, 91.

58. (a) Adam, W.; Prein, M. *J. Am. Chem. Soc.* **1993**, *115*, 3766. (b) Adam, W.; Nestler, B. *J. Am. Chem. Soc.* **1992**, *114*, 6549.

59. Henbest, H. B.; Wilson, R. A. *J. Chem. Soc.* **1957**, 1958. (b) Berti, G. *Top. Stereochem.* **1973**, 9, 93. (c) Hirayama, M.; Gamoh, K.; Ikeyama, N. *Tetrahedron Lett.* **1982**, *23*, 4725.

60. (a) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557. (b) Masaki, Y.; Hashimoto, K.; Serizawa, Y.; Koji, K. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3476.

61. Kutney, J. P.; Ratcliffe, A. H. *Syn. Comm.* **1975**, 47.

62. For mechanistic speculation regarding variations in stereoselectivity in organocopper additions to carbocyclic enones in the presence of trimethylsilyl chloride, see : (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015. (b) Horiguchi, Y.; Komatu, M.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 7087. (c) Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1990**, *31*, 1393. (d) Corey, E. J.; Boaz, N. W. *Tetrahedron* **1989**, *45*, 545.

63 Rubottom. G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599.

64. Hunig, S.; Wehner, G. *Synthesis* **1975**, 181.

65. (a) Toromanoff, E. *Bull. Soc. Chim. Fr.* **1962**, 708. (b) Delongshamps,P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; chapter 6.

66. (a) Jeroncic, L. O.; Cabal, M.-P.; Danishefsky, S. J.; Shuttle, G. M. *J. Org. Chem.* **1991**, *56*, 387. (b) For a study of the stereoselectivity of cuprate addition to acyclic γ-hydroxy-enones, see : Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc.* **1992**, *114*, 7652.

67. (a) House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1978**, *43*, 2443. (b) House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59. (c) Krauss, S. R.; Smith, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 141. (d) Hallnemo, J.; Olson, T.; Ullenius, T. *J. Organomet. Chem.* **1985**, *282*, 133.

68. Jones, A. B.; Yamaguchi, M.; Patten, A.; Danishefsky, S. J.; Ragan, J. A.; Smith, D.B.; Schreiber, S. L. *J. Org. Chem.* **1989**, *54*, 17.

69. Grieco, P. A.; Cooke, R. J.; Henry, K. J.; VandeRoest, J. M. *Tetrahetron Lett.* **1991**, *32*, 4665

70. (a) Crimmins, M. T.; Bankaitis-Davis, D. M.; Hollis, W. G. *J. Org. Chem.* **1988**, *53*, 652. (b) Zhao, S. K.; Helquist, P. *Tetrahedron Lett.* **1991**, *32*, 447. (c) Goodwin, T. E.; Rothman, N. M.; Salazar, K. L.; Sorrets, S. L. *J. Org. Chem.* **1992**, *57*, 2469.

71. For the preparation of $CuBr{\bullet}SMe_2$, see House, H. O.; Chu, C. Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.

72. Horiguchi, Y.; Satoshi, M.; Eiichi, N.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025.

73. Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

74. Ihara, M.; Yasui, K.; Tamiguchi, N.; Fukumoto, K. *J. Chem. Soc. Perkin Trans.1*, **1990**, 1469.

75. Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

76. (a) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703. (b) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. G.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241

77. (a) Moriya, O.; Okawara, M.; Ueno, Y. *Chem. Lett.* **1984**, 1437. (b) Ali, A.; Harrowver, D. C.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 2851.

78. Reppe, W. *Ann.* **1955**, *596*, 74.

79. Gousseaume, L. B. B.; Langwost, B. *Tetrahedron Lett.* **1989**, *30*, 4525.

80. Marvel, C. S.; Dec, J.; Cooke, Jr. H. G.; Cowan, J. C. *J. Am. Chem. Soc.* **1940**, *62*, 3495.

81. (a) Curran, D.P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746. (b) Curran, D. P.; Chang, C. T. *J. Org. Chem.* **1989**, *54*, 3140.

82. (a) Solomon, M.; Jamison, C. L.; McCormick, M.; Liotta, D. C.; Cherry, D. A.; Mills, J. E.; Shah, R. D.; Rodgers, J. D.; Maryanoff, C. A. *J. Am.*

Chem. Soc. **1988**, *110*, 3702. (b) Swiss, K. A.; Liotta, D. C.; Maryanoff, C. A. *J. Am. Chem Soc.* **1990**, *112*, 9393. (c) Swiss, K. A.; Hinkley, W.; Maryanoff, C. A.; Liotta, D. C. *Synthesis* **1992**, 127.

83. Nicolau, K. C.; Magolda, R. L.; Sipio, W. J.; Barnette, W. E.; Lysenko, Z.; Joullie, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 3784.

84. Bartlett, P. A. In "*Asymmetric Synthesis*"; Morrison, J. D., Ed.; Academic Press: New York, 1984; Chapter 6, Vol 3.

85. Corey, E. J.; Nicolau, K. C.; Shibasaki, M.; Machida, Y.; Shiner, C. S. *Tetrahedron Lett.* **1975**, 3183.

86. Torisawa, Y.; Okabe, H.; Ikegami, S. *Chem. Lett.* **1984**, 1555.

87. Larson, S. D.; Monti, S. A. *J. Am. Chem. Soc.* **1977**, *99*, 8015

88. Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.

89. Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63

90. Corey, E. J.; Singh, A. K.; Bakshi, R. K. *J. Am. Chem. Soc.* **1987**, *109*, 6187.

91. Demuth, M.; Mikhail, G.; George, M. V. *Helv. Chim. Acta* **1981**, *64*, 2759

92. Huffman, J. W.; Desai, R. C.; LaPrade, J. E. *J. Org. Chem.* **1983**, *48*, 1474.

93. (a)Bonadies, F.; Fabio, R. D.; Gubbiotti, A.; Mecozzi, S.; Bonini, C. *Tetrahedron Lett.* **1987**, *28*, 703. (b) For a reducing system based on titanium tetrachloride and lithium aluminum hydride, see Barluenga, J.; Resa, J. G.; Olano, B.; Fustero, S. *J. Org. Chem.* **1987**, *52*, 1425.

94. (a) Pedersen, S. F.; Dewan, J. C.; Eckman, R. R.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 1279. (b) Corey, E. J. *J. Org. Chem.* **1990**, *55*, 1693

95. Kim, S.; Ahn, K. H. *J. Org. Chem.* **1984**, *49*, 1717.

96. Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1876.

97. Waston, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

98. Curran, D. P.; Chang, C.-T. *J.Org. Chem.* **1989**, *54*, 3140.

99. Turos, E.; Audia, J. E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 8231.